

BEFORE THE STATE BOARD OF PHARMACY

STATE OF COLORADO

Case No. 2011-3973

CEASE AND DESIST ORDER

IN THE MATTER OF THE UNAUTHORIZED AND UNLAWFUL DISTRIBUTION OF
PRESCRIPTION DRUGS AND/OR COMPOUNDED PRESCRIPTION DRUGS IN
COLORADO BY NEW ENGLAND COMPOUNDING CENTER, INC.,

Respondent.

Pursuant to guidance established by the Colorado State Board of Pharmacy ("Board") at its January 15, 2009 meeting, documentation has been considered, including, but not limited to, the written complaint dated April 13, 2011, 2011, in the above-captioned matter.

Based upon this review, the Board hereby finds that it has jurisdiction over Respondent and the subject matter herein, and that there exists credible evidence that Respondent has acted without the required license or registration, in violation of §12-22-130(2) and 12-22-802, C.R.S.

The Board finds as follows:

1. Respondent's location at 697 Waverly St, Framington, MA 01702 is licensed or registered with the Board as a nonresident prescription drug outlet to dispense and deliver prescription drugs and/or compounded prescription drugs in the State of Colorado pursuant only to valid, patient-specific prescription orders.

2. Respondent's location at 697 Waverly St, Framington, MA 01702 is not licensed or registered to distribute stock prescription drugs and/or compounded prescription drugs in the State of Colorado.

3. On or around January 17, 2011 and March 24, 2011, Respondent distributed a stock compounded prescription drug from 697 Waverly St, Framington, MA 01702 to a prescription drug outlet in the State of Colorado.

4. Respondent's conduct constitutes the unlawful distribution of prescription drugs into the State of Colorado, in violation of §12-22-130(2) and 12-22-802, C.R.S.

WHEREFORE, pursuant to §12-22-125.2(9), C.R.S., the Board hereby ORDERS that Respondent immediately CEASE AND DESIST in engaging in the unlawful distribution of prescription drugs in the State of Colorado, in violation of §§12-22-130(2) and 12-22-802, C.R.S.

Within ten days after service of this order to cease and desist, Respondent may request a hearing on whether such acts or practices in violation Article 22 of Title 12, C.R.S. have occurred. Such hearing shall be conducted pursuant to §§24-4-104 and 24-4-105, C.R.S.

The Board authorized the undersigned representative to sign this Cease and Desist Order on its behalf.

DATED this 15th day of April, 2011.

STATE BOARD OF PHARMACY

BY: Wendy Anderson

Wendy Anderson
Program Director
1560 Broadway, Suite 1300
Denver, Colorado 80202

*February 24, 2003 – FDA Memorandum Detailing Meeting
Between FDA and the Mass. Bd. Regarding Recent
Complaints and Inspections (FEI # 3003623877)*



CE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

NEW ENGLAND DISTRICT
MEMORANDUM

Date February 24, 2003

From Kristina Joyce, Consumer Safety Officer, NWE-DO / FDA
Mark Lookabaugh, Compliance Officer, NWE-DO / FDA

Subject February 5, 2003 Meeting with Massachusetts Board of Pharmacy /
Division of Professional Licensure (239 Causeway Street, Boston, MA 02114).

To Central File

Firm: New England Compounding Center
697 Waverly Street
Framingham, MA
FEl: 3003 623 877

Background

This meeting was arranged at the request of Mark Lookabaugh, NWE-DO Compliance Officer, via email to Charles Young, Executive Director, on January 30, 2003. The meeting was held to review the inspectional history of the New England Compounding Center and develop a joint strategy for achieving safe compounding practices at the firm.

In attendance at the meeting were:

Representing the New England District—

Gail Costello, District Director
David Elder, Compliance Branch Director
Mark Lookabaugh, Compliance Officer
William Boivin, Supervisory Consumer Safety Officer
Kristina Joyce, Consumer Safety Officer

Representing the Office of Compliance, CDER (via teleconference)—

Fred Richman, OC / DNDLC
Kathleen Anderson, OC / DNDLC
Betty Hiner, ORO / DFSR

Representing the Commonwealth of Massachusetts—

Jean Pontikas, Director, Division of Professional Licensure
Charles Young, Executive Director, Board of Pharmacy
James Coffey, Associate Director, Board of Pharmacy
Lésle Doyle, Supervisory Investigator, Board of Pharmacy
James Emery, Investigator, Board of Pharmacy
Susan Manning, Legal Counsel, Board of Pharmacy

Note: This memorandum has been prepared in accordance with Staff Manual Guide FDA 2126.2

Summary of Meeting

Mr. Young and Mr. Lookabaugh facilitated introductions.

Mr. Lookabaugh began with an overview of the inspectional history of New England Compounding Center (NECC). This included a brief description of the recent regulatory history of Pharmacy Compounding.¹

William Boivin and Kristina Joyce then presented a table summarizing the results of FDA's current sample analyses.² Mr. Boivin and Ms. Joyce discussed current investigational findings.³ It was stated that the FDA's next step would be to notify the firm of the violative sample results and inquire of his intentions regarding the violative product still in commerce. It was anticipated that the firm would initiate a voluntarily recall of the violative product.⁴ If NECC does not take action regarding the violative lot, then depending on the quantities of the lot available FDA may initiate a seizure of the product. A Form FDA-483 (List of Inspectional Observations) will be issued to NECC with state representatives present at the FDA closeout meeting with NECC. Fred Richman and Kathleen Anderson reminded everyone that in a similar situation with a South Carolina compounding pharmacy, FDA issued a press release when the firm failed to take recall action in a timely manner.

A discussion was held to decide if NECC should be considered a manufacturer or a compounder. It was decided that current findings supported a compounding role. The FDA discussed their ability to take action (through seizure) against the adulterated lot of Betamethasone that is still within expiry. The issues of NECC's poor compounding practices would not necessarily be ultimately resolved by such an action. It was decided that the state would be in a better position to gain compliance or take regulatory action against NECC as necessary. The state favored recall of the violative product

¹ See Attachment 1.

² See Attachment 2.

³ See Form FDA-483 (Inspectional Observations), Attachment 3.

⁴ The firm has committed to recall this product.

within expiry. The state does not have the authority to subpoena records without cause or to embargo product, but agencies within their umbrella may be able to provide assistance in those matters. The state would ask Mr. Cadden, owner of NECC, to appear before the Board of Pharmacy to answer to the current complaints.

Leslie Doyle stated that NECC is licensed as a pharmacy provider in the following states—South Carolina, Florida, Virginia, Missouri, Maine, Rhode Island, New Hampshire, Nebraska, Idaho, and Montana. NECC is pursuing licensure in Connecticut, Ohio, Vermont, and Kansas.

Susan Manning stated Massachusetts pharmacy law states that pharmacists must act in accordance with USP recommendations. She stated this alone would imply he could be held to those standards by the state. She requested of the FDA a list of the current inspectional observations and where NECC differs from acceptable practice per USP standards. It was decided that Ms. Anderson would work on documenting the deviations from USP standards for the state. Ms. Manning stated although the state's authority does not include the ability to fine pharmacists, the state is able to take actions against a pharmacy's license, including revocation and suspension.

The state's pharmacy compounding regulations that are under review are a blend of USP standards and regulations from three other states that already have such regulations in place (including Georgia and South Carolina).

The state requested the following information⁵ from the FDA:

- Examples of previous Consent Agreements
- MedWatch reports regarding Adverse Events from products compounded by NECC.
- A list of NECC deviations from acceptable practice (referring to FDA's inspectional findings)
- Previous and current FDA 483 (List of Observations) issued to NECC, with available documentation to support the findings.
- Copies of FDA EIRs for NECC (April 2002 and current inspection when available)
- Analytical Worksheets for sample collection and analysis.
- Copy of regulatory action taken by the FDA against Professional Compounding Centers of America (PCCA).

Summary.

Mr. Elder concluded the meeting by summarizing the discussions and emphasizing the potential for serious public health consequences if NECC's compounding practices, in particular those relating to sterile products, are not improved. The point was made that, so long as a pharmacy's operations fall within the scope of the practice of pharmacy (as

⁵ This information was forwarded to the Board of Pharmacy (to the attention of Ms. Manning) via Federal Express on February 11, 2003.

outlined in FDA's Compliance Policy Guide 460.200), FDA will generally continue to defer to state authorities for regulatory oversight. In such cases FDA will seek to engage cooperative efforts aimed at achieving regulatory compliance and ensuring the safety and quality of compounded products.

Kristina Joyce
Consumer Safety Officer
New England District, FDA

Mark Lookabaugh
Compliance Officer
New England District, FDA

Attachments (3)

bcc:

MCL

KMJ

DKE

Central File

Reading File

Legal Reading File

Richman (HFD-310)

Anderson (HFD-310)

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ATTACHMENT 1

INSPECTIONAL HISTORY OF NEW ENGLAND COMPOUNDING CENTER (NECC)

Presentation to Board of Registration in
Pharmacy, Division of Health
Professions Licensure, Department of
Public Health, Commonwealth of
Massachusetts

February 5, 2003

April 2002

- New England District receives inspection assignment from CDER / Office of Compliance / DPDSC. Two MedWatch reports implicated product compounded at NECC in adverse events (dizziness, shortness of breath, diaphoresis, drop in blood pressure to 55/44).
- Product in question is Betamethasone Repository 6 mg/ml (Betamethasone Acetate 3mg/ml / Betamethasone Sodium Phosphate 3 mg/ml USP), available commercially as Celestone Soluspan.

April 2002

- This is the same formulation that was involved in 13 hospitalizations (including 5 cases of meningitis, 3 of which were fatal) and was compounded at Doc's Pharmacy in Walnut Creek, CA.

■ As a result of this incident the Atty General of California brought a formal accusation (on behalf of the Exec. Officer of the Board of Pharmacy) before a judge.

April 2002

- FDA team, along with Leslie Doyle of BRP conducted an inspection of NECC.
- FDA issues list of observations (Form 483).
- BRP pursues independent follow-up

July 2002 (and ongoing)

- Second inspection assignment is received from CDER as a result of 2 additional MedWatch reports associated with another product from NECC, in this case Methylprednisolone Acetate Suspension (Injectable, Preservative Free), 80 mg/ml.

- Both patients were hospitalized (pain, headache) and recovered. Units from suspect lot were collected from a ^{(b) (6); (b) (7)(c)} hospital.

July 2002 (and ongoing)

- Assistance of BRP requested as before.
- Section 503A of FDCA has since been invalidated by U.S. Supreme Court
- Inspection is initiated in August. Multiple samples are collected.

July 2002 (and ongoing)

- Urgent Care, Spartanburg, SC.

- On September 16, 2002 there is a recall of Methylprednisolone Acetate Injection compounded by this pharmacy as a result of fungal meningitis (4 patients contract this infection, 1 dies).
- Nationwide alert issued by FDA on November 15, 2002 for all injectable products produced by Urgent Care.
- Cease and desist order is issued by SC Board of Pharmacy.

July 2002 (and ongoing)

- Urgent Care, Spartanburg, SC.
 - MMWR (CDC, December 13, 2002) publishes assessment of this incident (*Exophiala* infection from Contaminated Injectable Steroids Prepared by a Compounding Pharmacy — United States, July–November 2002).

January 2003

- Samples with significant findings
 - 193610 *Burkholderia cepacia* and *Sphingomonas paucimobilis* (Methylprednisolone Acetate Injection)
 - 169127 Subpotency (Betamethasone Repository)
Expired on Jan 29, 2003
 - 169129 Subpotency (Betamethasone Repository)
Expires on June 8, 2003. *This product is adulterated under Sec. 501(b) of FDCA.*
 - 169128 Superpotency (Methylprednisolone Acetate Injection) Expired on Jan 10, 2003

Existing Concerns

- Analytical evidence demonstrates inability of NECC to reliably compound suspensions with dose uniformity.
- Sterilization techniques and aseptic practices continue to raise questions, despite no positive (nonsterile) results from latest samples. Absence of evidence is not evidence of absence.

ATTACHMENT 2

SUMMARY OF SAMPLE COLLECTION/ANALYSIS FOR NECC
FEBRUARY 5, 2003

<u>SAMPLE</u>	<u>PRODUCT</u>	<u>LOT</u>	<u>QTY</u>	<u>Exp</u>	<u>Results</u>
169123	Methylprednisolone AC (PF) 80 mg/ml x 1 ml	11262002@4	20	1/25/03	Assay= Within Range
169127	Betamethasone Repository (PF) 6mg/ml x 5ml (BSP+BA)	11302002@1	10	1/29/03	Assay= Subpotent BSP 77.4 (O); 74.6 (C/A) BA 71.6 (O); 71.0 (C/A)
169128	Methylprednisolone AC (PF) 40 mg/ml x 1 ml	11262002@5	50	1/10/03	Sterility= Negative Endotoxin= "not performed" Assay= Superpotent 131.4 (O) & 133.1% (C/A)
169129	Betamethasone Repository 6mg/ml x 2 ml	12102002@1 1	50	6/8/03	Sterility= Negative Endotoxin= Negative Assay= subpotent BSP 67.0 (O); 62.0 (C/A) BA 59.8 (O); 58.7 (C/A)
169130	Methylprednisolone AC (PF) 80 mg/ml x 1 ml	11262002@4	50	1/25/03	Sterility= Negative Endotoxin= Negative
169131	Triamcinolone Acetonide 40 mg/ml x 5 ml	112020002@ 8	34	2/18/03	Sterility= Negative Endotoxin "not performed"
169132	Prochlorperazine Edisylate 5 mg/ml x 10 ml	11112002@1 1	18	2/9/03	Sterility= Negative Endotoxin "not performed"
169133	Saline PF 10% injectable x 15 ml	12122002@1 4	5	3/12/03	Sterility= Negative Endotoxin= "not performed"
208553	Betamethasone Repository (PF) 6mg/ml x 2ml	11302002@1	50	1/29/03	Sterility= Negative Endotoxin= "not performed"
	Sterile Vials				
	Vial stoppers				

1. PF= Preservative Free (for some products, NECC makes product both with and without preservative)
2. Betamethasone Repository= Betamethasone Sodium Phosphate & Betamethasone Acetate.

<u>SAMPLE</u>	<u>PRODUCT</u>	<u>LOT</u>	<u>QTY</u>	<u>Exp</u>	<u>Results</u>
193610 (9/13/02)	Methylpredisalone AC (PF) 80MG/ML INJ		16		1/14= <i>Sphingomonas paucimonas</i> 4/14= <i>Burkholderia cepacia</i>

SUMMARY OF FDA INSPECTIONAL OBSERVATIONS FOR NECC
FEBRUARY 5, 2003

ASSAY ISSUES

- 1) No documentation to verify sterile drug products meet set standards, such as:
 - a. No specifications (ie. USP or other) are set for finished products
 - b. No evidence products meet assigned shelf life.
- 2) Preparation: No documentation of the following:
 - a. Equipment used to measure components are calibrated and maintained to perform their intended function
 - b. Preparation steps are being performed in a correct manner since batch record preparation instructions are lacking significant preparation steps, including mixing and transfilling procedures.
 - c. All components (drug substances, water, vials, rubber stoppers) meet set standards making them suitable for their intended use and don't contaminate the finished product.
 - d. Testing and sampling procedures performed for finished drug products are representative of the lots/batches being tested.
- 3) Testing/Sampling: No documentation of the following
 - a. No testing is done to confirm product meets specifications. (the only finished product testing for selected lots is sterility and endotoxin).
 - b. Testing and sampling procedures performed for finished drug products are representative of the lots/batches being tested.

STERILITY ISSUES

- 1) Lack of assurance/documentation:
 - a. Equipment, supplies and workspaces are sufficiently cleaned to prevent contamination of finished product.
 - b. No Environmental Monitoring of Clean Room.
 - c. All autoclave sterilization processes are suitable for the sterilization of drug product preparation equipment and components.
 - d. Transfer of bulk drug product and equipment from the autoclave (from one room thru ante-room to "clean room") for further processing doesn't contaminate product.
 - e. Transfilling procedures are being performed in a correct manner since batch record preparation instructions lack transfilling instructions.

ATTACHMENT 3

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

One Monivie Avenue, 4th Floor
Stoughton, MA 02180
(781) 596-7700

DATE(S) OF INSPECTION

10/24, 12/12&18/02, 1/14-15/03, 2/10/03

FED NUMBER

3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

Mr. Mark J. Gifford, Director of Pharmacy

FIRM NAME

New England Compounding Center

STREET ADDRESS

697 Waverly Street

CITY, STATE AND ZIP CODE

Frammingham, MA 01702

TYPE OF ESTABLISHMENT INSPECTED

Pharmacy

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

The below observations pertain to drug products that personnel prepare at your firm for which you claim are sterile (for example, injections) and are prepared in anticipation of a prescription.

- I. For the preparation of sterile drug products distributed by your firm (such as those intended for injection), there is no adequate documentation available to verify they meet set standards (such as specifications and/or USP limits if applicable) or the shelf life (expiration dating period) of these products. This includes the absence of documentation to verify the following:
 - A. Personnel performing preparation steps are not contaminating the finished products.
 - B. Workspaces are cleaned and sanitized to prevent product contamination.
 - C. Equipment and supplies entering the product preparation area are decontaminated/cleaned to prevent product contamination.
 - D. The environment in the area where the filling and closing operations are performed is adequate to prevent product contamination (this includes the lack of documentation pertaining to environmental monitoring in the immediate area while product is exposed to the environment, such as during filling and prior to container closure).
 - E. All autoclave sterilization processes are suitable for the sterilization of drug product preparation equipment and components (which includes vial stoppers and bulk product). Some examples are:
 - a. Lack of documentation to verify that all critical processing parameters being used are appropriate in ensuring that final products meet all standards (such as sterility). Critical processing parameters include sterilization time, temperature, size and nature of load, and chamber loading configuration.
 - b. Records do not state the actual critical parameters used during processing.
 - c. Lack of documentation to verify that the autoclave itself is maintained and calibrated to perform its intended function.
 - d. The autoclave process used on bulk drug products does not have an effect on stability or product specifications.
 - F. The transfer of bulk drug product and equipment from the autoclave (after it went through an autoclave process) from one room to another room in which further preparation steps are performed in a laminar air flow workbench, is not introducing contamination into the finished product. All components, including drug substances, vials, and rubber stoppers, meet set standards making them suitable for their intended use.
 - G. Components and process water are not contaminating finished products.
 - H. Equipment used to measure the amount of ingredients/components are calibrated and maintained to perform their intended function.
 - I. Testing procedures and sampling procedures being performed for all drug products are representative of the lots/batches being tested.
 - J. That for each preparation of a sterile product or batch of sterile products there has been appropriate laboratory

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EMPLOYEE(S) SIGNATURE

EMPLOYEE(S) NAME AND TITLE (Print or Type)

DATE ISSUED

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

One Monivale Avenue, 4th Floor
Stoughton, MA 02180
(781) 596-7700

DATE(S) OF INSPECTION

10/24, 12/12, 18/02, 1/14-15/03, 2/10/03

FEI NUMBER

3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

Dr. Robert J. Cohen, Director of Pharmacy

FIRM NAME

New England Compounding Center

STREET ADDRESS

697 Waverly Street

CITY, STATE AND ZIP CODE

Framingham, MA 01702

TYPE OF ESTABLISHMENT INSPECTED

Pharmacy

determination of conformity with purity, accuracy, sterility, and non-pyrogenicity, in accordance with established written specifications and policies.

- K. Preparation steps are being performed in a correct manner since batch record preparation instructions are lacking significant preparation steps, which includes mixing procedures.
- L. Final containers are capable of maintaining product integrity (i.e. identity, strength, quality, and purity) throughout the shelf life of the product.
- M. All drug products prepared and packaged at your site meet specifications and USP limits (if applicable) for the expiration dating period assigned. According to documentation and your statements, all drug products are assigned an expiration date of 60 days if they do not contain a preservative, three months if they are not filtered, and 6 months if they are filtered. No data was available for any of your products prepared at your firm to support these expiration date periods.

In addition, for all of the items above there were no written procedures available pertaining to the performance of these duties and processes.

- 2. There are no written procedures pertaining to the handling of complaints, nor does your firm maintain a complaint file.
- 3. There was no documentation available for the handling and disposition of reports of patient problems, complaints, adverse drug reactions, drug product or device defects, and other adverse events reported. For example, after a medical facility reported adverse events associated with lot 05312002@16, your firm conducted a recall of injectable steroid products and implemented shorter expiration dates and use of pre-sterilized vials. You stated you have no documentation available pertaining to an investigation being performed for this and other related lots which shows that adequate follow-up action was taken.

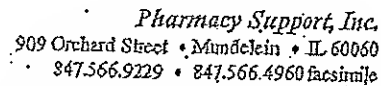
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EMPLOYEE(S) SIGNATURE

EMPLOYEE(S) NAME AND TITLE (Print or Type)

DATE ISSUED

*January 30, 2006 – Initial Report From PSI to NECC
(Dockets DS-03-055/PH-03-066 and DS-05-040)*



Docket Nos: DS-03-055
PH-03-066
DS-05-040

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BOARD OF REGISTRATION
IN NURSING

It was our pleasure meeting with you and your colleagues during our visit last week. We acknowledge and appreciate the time and effort put forth from everyone at the facility to complete this assessment in the time allotted.

The purpose of our visit was to conduct an assessment of your facility located at 697 Waverly Road, Framingham, MA. It is our understanding that the State Board of Pharmacy required this assessment be conducted by a Board-approved evaluator analyzing your compounding practices and compliance with United States Pharmacopoeia Standard <795>, non-sterile compounding procedures and USP standard <797>, sterile compounding procedures, with recommendations for revisions to practices for compliance with the USP standards. The state board approved Pharmacy Support, Inc as the evaluator.

~~_____~~ The assessment was conducted January 17 and 18, 2006.

The assessment covered the following areas for sterile compounding:

- Sterile Environmental Design
- Quality Assurance Program
- Media Fills (Process Validation/Operation Qualifications)
- Environmental Monitoring Program
- Cleaning and Sanitization Program
- Training Program
- Process Control
- Equipment
- Finished Preparation Testing
- Adverse Event Records
- Deviation/OOS Reports, Investigations and Corrective Action Process
- Complaint Handling Program
- Standard Operating Procedures

- Personnel
- Raw material control and testing
- Compounding preparations
- Validation of critical processes
- Environmental Monitoring
- Beyond Use Dating
- Standard Operating Procedures
- Investigations and Documentation



Pharmacy Support, Inc.
909 Orchard Street • Mundelein • IL 60060
847.566.9229 • 847.566.4960 facsimile

Positive Comments

The newly installed modular clean room is state of the art and is of sufficient size and design for proper operation and to prevent contamination.
The facility is of suitable size and construction to facilitate cleaning, maintenance, and proper operations.
Personnel interviewed have appropriate education or experience to perform assigned functions.
There are an adequate number of employees to perform and supervise the compounding operations.
Equipment utilized is appropriate for compounding operations.
All lots of products are compounded in accordance with a prescription.

Conclusion

Although your facility has seen significant upgrades in facility design for the sterile compounding operation, there were numerous significant gaps identified during the assessment therefore, it is the opinion of the auditors that your operation needs to be upgraded and enhanced to be in substantial compliance with United States Pharmacopeia <795> or <797>. The auditors observed some of the compounding activities and although the technicians appeared to be performing the operation adequately, without a written procedure to follow it is not known if the activity is repeatable and reliable; and as noted throughout the report much of the documentation for the activities that is performed is inadequate. Upon implementation of the recommended corrective actions, we believe that appropriate systems will be in place and in compliance with the USP standards. The recommended corrective actions are intended to address the systemic issue and not necessarily the isolated instances of non-compliance. The recommended corrective actions can be implemented in the specified time frame requested from the State Board of Pharmacy.

Major areas of concerns:

- Inadequate/incomplete documentation i.e. Good Documentation Practices are inadequate.
- Written procedures are admittedly not routinely followed and/or Sop's are not written.
- In many cases the procedures are not in strict accordance with USP <795>/<797>.
- End product testing is often performed on "stock solutions" and not the end product that is required.
- Process controls including validation of sterilization cycles and media fills are inadequate.

In a continuing effort to help keep management in compliance with the USP standards, PSI is recommending that you consider hiring a qualified Quality Assurance professional who would take responsibility for maintenance of the newly developed quality systems.

The assessment results have been included for your review. The results have been formatted into three sections: 1) specific USP requirement, 2) observation or non-compliance to each USP requirement highlighting specific examples as evidence of the non-compliance and 3) recommended corrective action.

Sincerely,

M. Moriva

Mick Moriva
V.P. Quality Operations
Pharmaceutical Systems, Inc.

cc: The Massachusetts Board In Registration in Pharmacy
Ross A. Caputo, Ph.D., Pharmacy Support, Inc.
Megan Jeffrey, Pharmacy Support, Inc.

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

Company Name: New England Compounding Center

Company Contact: Greg Coniglaro and Barry Cadden

Phone: 508-820-0606



Observations requiring Corrective Action

Non-Sterile Compounding

Note: As discussed with the Director of Pharmacy, this section of the USP requirements has not been addressed by New England Compounding Center as no current active procedures exist. Focus has been directed to the sterile side of the operation. By reviewing the Standard Operating Procedure index, the auditors observed that although there are some procedures, the majority of them are not written explicitly for meeting the requirements of USP <795>. None of the SOP's that are written for the non-sterile operation are signed or approved. The list below is not intended to be all inclusive of the requirements of USP <795>, but the entire section of standards needs to be addressed formally.

Requirement - USP <795> - Responsibility of the Compounder

"Personnel are capable and qualified to perform their assigned duties."

Observations 1

a) There is no written/documented procedure (SOP) defining a training program for non-sterile compounding personnel.

b) There is no documentation of training conducted.

Recommendations

Establish a formal training program. Document requirements of the training program in an SOP.

Perform training in accordance with the requirements

Document all training conducted

Conduct performance reviews at scheduled intervals to assure that processes continue to be carried out in accordance with written procedures. Written and practical exams should be considered

Observation 2

a). There is no written standard operating procedure to define the roles and responsibilities of the compounder (pharmacist as defined in <1075> and <795>) to assure quality is built into the products to include key factors as outlined in the standards.

- o Example: No written procedures to assure critical processes are validated, No written procedure for stability program, No written procedure detailing quality verifications to assure no compounding errors have occurred.

Recommendations

Formal standard operating procedures must be written to address compounder's roles and responsibilities including all key factors as described in the standards.

Requirement - USP <795> - Compounding Environment

"Areas designated for compounding have adequate space for the orderly placement of equipment and materials to prevent mix-ups between ingredients, containers, labels, in-process materials, and finished preparations. The compounding area is also to be designed, arranged, used, and maintained to prevent adventitious cross-contamination."

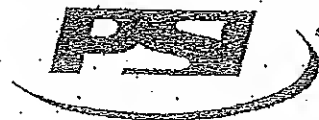
"Equipment and accessories used in compounding are to be inspected, maintained, cleaned, and validated at appropriate intervals to ensure the accuracy and reliability of their performance."

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

Company Name: New England Compounding Center

Company Contact: Greg Conigliaro and Barry Cadden

Phone: 508-820-0606



Requirement - USP <795> - Ingredient Selection

"Only manufactured drugs from containers labeled with a batch control number and a future expiration date are acceptable..."

Observation 5

- a) Ingredients were transferred to a secondary container with insufficient labeling.

Recommendation

Label all bottles and pre-mix syringes appropriately.

Requirement - USP <795> Compounded Preparations

"Unless otherwise indicated or appropriate, compounded preparations are to be prepared to ensure that each preparation shall contain not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of active ingredient per unit weight or volume and not less than 90% and not more than 110% of the theoretically calculated weight or volume per unit of the preparation"

Observation 6

- a) There is no written SOP defining release criteria to verify that each preparation shall contain not less than 90% and not more than 110%.

Recommendation

Establish a release program to verify preparation accuracy.

Requirement - USP <795> Compounding Process

"The compounders are to consider using the following steps to minimize error and maximize the prescriber's intent..."

Observation 7

- a) No requirements for donning proper attire or hand washing.
- b) There is no written SOP defining the final appearance of the formulation as part of release of the preparation.

Recommendation

Author SOP defining proper attire and hand washing.

Establish a program to verify release criteria including final appearance of formulation.

Requirement - USP <795> - Compounding Records and Documents

"This record must list the name, strength, and dosage form of the preparation compounded, all ingredients and their quantities, equipment needed to prepare the preparation, when appropriate, and mixing instructions. Mixing instructions should include the order of mixing, mixing temperatures or other environmental controls, such as duration of mixing, and other factors pertinent to the replication of the preparation as compounded. The formulation must include the beyond-use date, the container used in dispensing, the storage requirements and any quality control procedures."

Observation 8

- a) The formulation record is incomplete and/or not appropriately designed

Example:

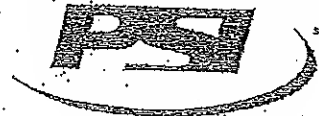
- Equipment description or equipment number is not identified;
- The mixing instructions are not specific and do not always indicate time and temperature.

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

Company Name: New England Compounding Center

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Phone: 508-820-0606



- Environmental controls are not specified
- No quality control procedures are defined

Recommendations:

List equipment and any other instruments on formulation record.

Update mixing instructions with ranges and times:

- o Cover while stirring.
- o Example of an adequate mixing instruction, "The compound should be mixed on the hot plate at 75°C +/- 10°C for 10-15 minutes. Document temperature and time on compounding record."

List all safety, identity, strength, quality and purity information as applicable to the finish preparation.

Requirement - USP <795> - Quality Control

"To ensure accuracy and completeness, the compounder is to observe the finished preparation to ensure that it appears as expected and is to investigate any discrepancies and take appropriate corrective action..."

Observation 9

a) There are no CAPA (Corrective Action and Preventative Action) or OOS (Out of Specification) /investigation SOPs written.

Recommendation

Develop CAPA and OOS/Investigation SOPs

Requirement - USP <795> - Verification

"The act of verification of a compounding procedure involves checking to ensure that calculations, weighing and measuring, order of mixing, and compounding techniques were appropriate and accurately performed."

Observation 10

a) There are no written procedures for finished preparation verification or release of preparation. Checks do not include ingredient, lot number, or expiration check.

Recommendation

Develop a finished preparation SOP

Develop a release SOP that requires specific verifications and the documentation requirements.

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

Company Name: New England Compounding Center
Company Contact: Greg Conigliaro and Barry Cadden
Phone: 508-820-0606



Sterile Compounding

Requirement - USP <797> - Responsibilities of all compounding personnel

"Opened or partially used packages of ingredients for subsequent use in CSPs are properly stored under restricted access conditions in the compounding facility. Such packages cannot be used when visual inspection detects unauthorized breaks in the container, closure, and seal; when the contents do not possess the expected appearance, aroma, and texture; when the contents do not pass identification tests specified by the compounding facility; and when either the beyond-use or expiration date has been exceeded."

"Measuring, mixing, sterilizing, and purifying devices are clean, appropriately accurate, and effective for their intended uses."

Observations 1

- a) No documentation of inspection of incoming materials.

Recommendations

Develop a written procedure for incoming inspection of raw materials.

Observation 2

- a) Glassware/metal equipment used for CSPs is not depyrogenated before use.

Recommendations

Change SOP(s) to require depyrogenation of glassware where appropriate.

Depyrogenate all glassware/metal equipment before use.

Provide adequate storage space for depyrogenated glassware when not used immediately.

Requirement - USP <797> - Verification of Compounding Accuracy and Sterilization

Steam

"To achieve sterility, it is necessary that all materials be exposed to steam at 121°, under a pressure of about one atmosphere or 15 psi, for the duration verified by testing to achieve sterility of the items, which is usually 20 to 60 minutes for CSPs.... Sealed containers must be able to generate steam internally; thus, stoppered and crimped empty vials must contain a small amount of moisture to generate steam."

Observation 3

- a) No documentation exists for the evaluation of appropriate sterilization method.
- b) Sterilization equipment has not been verified.
- c) No verification that product reaches 121° for a minimum 15 minutes.
- d) Documentation of sterilization cycles is insufficient and/or incomplete.

Recommendations

Verify sterilization methods.

Record pressure and temperature with each cycle.

Verify load configurations.

Dry Heat

"Glass and metal devices may be covered tightly with aluminum foil, then exposed to dry heat in an oven at a mean temperature of 250° for 2 hours to achieve sterility and depyrogenation (see *Dry-Heat Sterilization* under *Sterilization and Sterility Assurance of Compounding Articles*, USP Chapter <1211>). Such items are either used immediately or stored until use in an environment suitable for compounding low- and medium-risk CSPs."

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

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Observation 4

- a) Depyrogenation of glassware is not performed or documented.
- b) No documentation for sterilization cycles.
- c) Sterilization equipment has not been verified.

Recommendations

Glassware used in high risk compounding must be depyrogenated and stored appropriately.
Verify sterilization methods.

Filtration

"Commercially available sterile filters must be approved for human-use applications in sterilizing pharmaceutical fluids. Both filters that must be sterilized before processing CSPs and those filters that are commercially available, disposable, sterile, and pyrogen-free have a nominal porosity of 0.2 μm , which includes 0.22- μm porosity".

"Personnel ascertain from appropriate information sources that the sterile microporous membrane filter used to sterilize CSP solutions, either during compounding or administration, is chemically and physically compatible with the CSP."

Observation 5

- a) Commercially available filter devices are not documented to be received with certification of analysis.
- b) No written procedure for sterilization by filtration.
- c) Bubble point test for integrity is not performed.
- d) Filter compatibility is not documented.

Recommendations

Retain Certificates of Analysis of filters for records.
Better documentation for sterilization by filtration.
Document and verify filter compatibility.

Requirement - USP <797> - Personnel Training and Evaluation in Aseptic Manipulation Skills

"Media-fill testing is used to assess the quality of the aseptic skill of compounding personnel. Media-fill tests represent the most challenging or stressful conditions actually encountered by the personnel being evaluated when they prepare particular risk level CSPs and when sterilizing high-risk level CSPs".

Observation 6

- a) Media fill acceptance criteria has not been defined.
- b) Corrective action for media fill failure has not been defined (performed).
- c) Media fill protocols are incomplete in that:
 - Media fill final reports documenting results are not completed.
- d) Appropriate interventions during media fills are not defined.
- e) No Environmental Monitoring taken during media fills.
- f) No growth promotion documentation of media fills media.
- g) Media fill procedures are inadequate and inconsistent.
- h) Process validation media fills do not contain the proper number of containers.

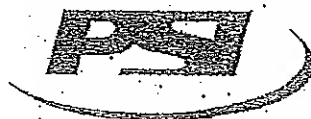
Recommendations

Process media fills mimic actual process.
Media-fills must be performed at the frequency defined in USP <797> (annual-low/medium, semi-annual-high).
Media-fill protocols should be established in that:

- EM sampling is conducted during the media fill. EM sampling must include sampling of personnel and surfaces as well as viable and non-viable air sampling.

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

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Company Contact: Greg Coniglaro and Barry Cadden
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- Media fill final reports should be written documenting results.
- Appropriate interventions during media fills need to be defined.
- Media fills cover multiple container/closure sizes.
- Corrective action for media fill failure needs to be defined.

Requirement - USP <797> - Environmental Quality and Control

"The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area should be smooth, impervious, free from cracks and crevices, and non-shedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate."

"Primary environmental control must provide at least ISO Class 5 quality of air to which sterile ingredients and components of CSPs are directly exposed."

"Only approved cleaning and sanitizing agents are used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues... In the anteroom area, supplies and equipment removed from shipping cartons are wiped with a sanitizing agent, such as sterile 70% Isopropyl alcohol (IPA), which is checked periodically for contamination."

"Personnel are critical keys to the maintenance of asepsis when carrying out their assigned responsibilities. They must be thoroughly trained in aseptic techniques and be highly motivated to maintain these standards each time they prepare a sterile product."

"Evaluation of environmental quality is performed by measuring both the total number of particles and the number of viable microorganisms in the controlled air environments of the compounding area."

Furthermore, "...the air sampling is performed at locations judged by compounding personnel to be the most prone to contamination during compounding activities: this includes zones of air backwash turbulence within LAFWs and other areas where air backwash turbulence may enter the compounding area."

Observation 7

- a) Schedule for cleaning is not as per USP <797>.
- b) Floors in the unclassified/hybrid buffer area have not been sanitized in 3 months of use.
- c) Shelving/cabinets adjacent to glove boxes have not been sanitized in 3 months of use.
- d) Stereo in hybrid buffer area.

Recommendations

Remove all unnecessary items from the hybrid buffer area i.e. stereo

Include all items in hybrid buffer area on the cleaning schedule.

- Floors should be mopped daily
- Shelving units should be cleaned weekly
- Walls and Ceilings should be cleaned monthly

Include shelving units on the cleaning schedule. They should be cleared off and wiped down.

Observation 8

- a) Compounding area not certified to be ISO Class 5 during dynamic conditions.
- b) Visible holes on glove box gloves. 4 out of the 8 gloves observed had holes while CSP was compounded.

Recommendations

All classified areas must be certified during dynamic conditions.

Observation 9

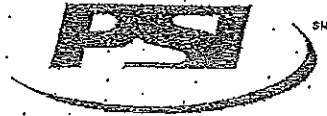
- a) Non-sterile 70% IPA is used to sanitize.
- b) Non-sterile 70% IPA is not periodically checked for contamination.

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

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Recommendations

Bleach or other appropriate sporocide should be used for cleaning on a weekly/quarterly basis, especially for incubators and refrigerators.
Utilize sterile 70%IPA.

Observation 10

- a) Hairnets and beard covers were not worn properly.
- b) Gowning procedure is not established.
- c) Beard covers not worn.
- e) Shoe covers not worn.

Recommendations

Personnel should be gown certified to work in the hybrid buffer area. This would include microbial samples of personnel.

Hairnets must cover all hair and ears.

Beard covers must be worn while compounding.

There should be a procedure for the cleaning of scrubs and lab coats.

Observation 11

- a) Environmental data is not documented properly.
- b) Environmental monitoring procedures are inadequate.
- c) Environmental monitoring procedures do not provide operator with instructions when there is an action level reached.

Recommendations

All class 100 / ISO-5 microbial recovery should be identified to the genus and species level.

Environmental monitoring program must include personnel fingertip plates.

Environmental monitoring procedure must be updated to include corrective actions for out of specification results.

Procedures for tracking and trending data need to be established.

Requirement - USP <797> - Processing Equipment

"It is necessary that equipment, apparatus, and devices used to compound a CSP are consistently capable of operating properly and within acceptable tolerance limits. Written procedures outlining required equipment calibration, annual maintenance, monitoring for proper function, controlled procedures for use of the equipment and specified time frames for these activities are established and followed."

Observation 12

- a) There is no written SOP's for calibration/preventative maintenance of autoclaves, dishwasher, isolator, freezers or Baxa pumps.
- b) Calibrations are not performed properly. Not verified against a certified standard
- c) No written preventative maintenance/cleaning schedules established for equipment.
- d) No written requirements/corrective actions established for out of tolerance readings.

Recommendation

Author SOPs that include equipment, use, maintenance and calibration.

Author SOPs to include cleaning schedules.

Requirements/corrective actions need to be defined and documented.

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

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Requirement - USP <797> - Finished Preparation Release Checks and Tests

"All high-risk level CSPs for administration by injection into the vascular and central nervous systems that are prepared in groups of more than 25 identical individual single-dose packages, or in multiple dose vials for administration to multiple patients, or are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized are tested to ensure that they are sterile (see Sterility Tests <71>) and do not contain excessive bacterial endotoxins (see Endotoxins <85>)."

"Finished CSPs are individually inspected in accordance with written procedures after compounding. If not distributed promptly, these products are individually inspected just prior to leaving the storage area. Those products that are not immediately distributed are stored in an appropriate location as described in the written procedures. Immediately after compounding and as a condition of release, each product unit, where possible, should be inspected against lighted white or black background or both for evidence of visible particulates or other foreign matter."

Observation 13

- a) Sterility testing is not being performed per USP <71>
- b) The testing laboratory has not been surveyed to ensure sterility and endotoxin testing is completed per the applicable USP methods, Sterility Tests <71>, Bacterial Endotoxin Test <85>, chemistry tests as applicable.

Recommendations

- Verify that sterility testing is conducted as per USP <71>.
- Sterility testing is contracted out to an outside laboratory, although not required, it is highly recommend that there be an audit of the facility to ensure their adherence to USP <797> and <71> requirements for testing.

Observation 14

- a) No written procedure for final inspection.
- b) No documentation of quarantined area.
- c) No documentation of release of preparation from quarantine.

Recommendations

Establish a final inspection procedure.
Author SOPs for quarantine and release of final preparations.

Requirement - USP <797> - Storage and Beyond-Use Dating

"Beyond-use dates for CSPs that are prepare strictly in accordance with manufactures/ product labeling must be those specified in that labeling, or from appropriate literature sources or direct testing."

Observation 15

- a) BUD assigned incorrectly.

Recommendations

Revise BUD assignment to reflect what is defined in USP <797> or provide stability studies.

Requirement - USP <797> - The Quality Assurance Program

"A provider of CSPs must have in place a formal Quality Assurance (QA) Program intended to provide a mechanism for monitoring, evaluating, correcting, and improving the activities and processes described in this chapter (USP <797>)."

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report.

Company Name: New England Compounding Center

Company Contact: Greg Conigliaro and Barry Cadden

Phone: 508-820-0606



Observation 16

- a) There are no written procedures for receipt, storage, and accountability of controlled substances.
- b) There is no written procedure for Good Documentation Practices.
- c) Good Documentation Practices are not followed.
- d) No written procedure for Deviations, Investigations and Corrective/Preventative Actions
 - When temperature monitoring was not performed/documented or temperature was out of range, there was no deviation opened, investigation or Corrective/Preventative action put in place.
- e) Failure/OOS procedures for final release are insufficient.
 - No investigation for finished preparation testing failures, i.e. potency was above specification and released.
- f) No written procedure for how to use/complete formula worksheets.
- g) No change control procedures
- h) SOPs are inadequate or not followed.

Recommendations

Develop a Quality System

Review all SOPs and revise to be applicable to current practice.

Observation 17

- a) The SOP for complaint handling is not followed. Investigations are not performed when required. Numerous blanks on all forms. RMA #'s not assigned and/or authorized by Pharmacy director.
- b) Complaint forms were not available for some complaints logged in the complaint log. Example: 2005-77.

Recommendation

Review current SOP for adequacy to assure responsibilities are clearly defined

Make necessary changes to procedures

Follow the procedure

Document complaints completely

Observation 18

- a) Lot numbers are not assigned appropriately. Multiple configurations filled from the same stock solution bear the same lot number. (2ml fill, 10ml fill etc).

Recommendation

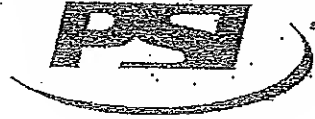
Establish a procedure for assigning unique lot numbers.

Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report

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Company Contact: Greg Conigliaro and Barry Cadden

Phone: 508-820-0606



General Documentation Observations

- Overall documentation practices are insufficient as evidenced by the following
 - Numerous empty spaces on forms and the use of "N/A" not noted when appropriate.
 - Many instances where documentation does not contain "Reviewed by/Dates" lines.
 - Most Log Sheets do not have a preformed by Initial/Date/Time.
 - Temperature Monitoring Logs do not have a space for the equipment that is being monitored.
 - Corrections are not performed properly with a single line out as to retain all data.
 - Most sections of complaint forms are not complete
 - Product Return tracking forms are incomplete and not authorized by the Pharmacy Director

Report Prepared by:

Meghan Duffrey

Date: 01-30-06

Reviewed by:

M. Mura

Date: 01-30-06



Pharmacy Support, Inc.
909 Orchard Street • Mundelein • IL 60060
847.658.9229 • 847.658.4860 facsimile

Results & Recommendations:

Oven

Manufacturer: YWR

Model: 1685

Serial: 02002506

Location: Storage Room

Two cycles were run to determine parameters to be programmed on the Oven's Watlow 981 controller. One cycle was run with the programmed parameters to verify minimum chamber's temperature of 250°C for 2 hours.

Results:

Load used for Temperature Verification

- 1 - 15 Liters beaker
- 1 - 10 Liters beaker ¼" thick
- 1 - 10 Liters beaker
- 1 - 5 Liters beaker
- 2 - 1.5 Liters beaker
- 1 - 2 Liters beaker

RUN 1

Temperature distribution data showed that the oven controller must be set to 262°C or higher in order to achieve a chamber temperature of 250°C or higher.

Load temperature distribution showed that the load located in the bottom shelf of the oven did not reach 250°C.

Actions:

- One of four shelves was removed from the oven.
- Large size pieces were moved from Bottom shelf to top shelf.
- Large to medium size pieces were placed on the medium shelf.
- Small size pieces were placed on the bottom shelf.
- A second run was performed.

RUN 2

Temperature distribution data showed that the oven controller set at 265°C achieved a chamber temperature of 250°C or higher.

Load temperature distribution showed that the load located in the bottom shelf of the oven did not reach 250°C.

Actions:

- Bottom shelf was raised approximately 10 inches from the bottom of the oven's chamber.
- Watlow controller was programmed base on run 1 and run 2 results.



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Program 1 of Watlow controller was executed.

RUN 3

Temperature distribution data showed that the oven achieved a chamber temperature of 250°C or higher for 1 hour and 30 minutes using the program with a soak set point of 265°C.

Load temperature distribution showed that the load reached 250°C.

Actions:

Program 1 of Watlow controller was edited for soak time. Original soak time of 2 hours and 15 minutes was replaced by 2 hours and 45 minutes in order to maintain a chamber temperature of 250°C or higher for two hours.

Recommended Action:

Install a chart recorder for temperature data collection when depyrogenation cycle is run.

Method:

Freezer:

Empty chamber temperature distribution using 6 thermocouples was performed.

Thermocouples were placed geometrically to monitor the workable space in the freezer's chamber.

Results & Recommendations:

Freezer

Manufacturer: Marvel Scientific

Model: 15AF0001

Serial: TE/111605001

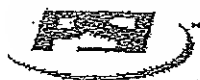
Location: Clean Room 1

Results:

Empty chamber temperature distribution was performed with the freezer's controller set to the maximum setting. Temperature data shows a minimum temperature of -27°C and a maximum temperature of -12°C. Since NECC uses this freezer to store drugs with a label of -20°C for storage, this freezer is suitable for this particular application. Any other drug substances intended for storage below -20°C should be treated on a case-by-case basis.

Recommended Action:

Evaluation of drug substances storage should be taken into consideration for temperature below -20°C.



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Method:

Autoclave sterilization:

"Wrapped Goods Cycle" 135°C for 10 minutes with a 15 minute drying time (Clean Room 1 autoclave).

VWR Autoclave located in clean room 1:

Wrapped Goods Cycle load

Load

- 1 - 7 1/2" x 13" stoppers bag with approximately 50 stoppers
- 3 - 7 1/2" x 13" stoppers bag with approximately 60 stoppers
- 2 - 5 1/4" x 10" stoppers bag with approximately 20 stoppers
- 1 - 7 1/2" x 13" bag with 15 - 3 1/2" x 8" bags

3M SteriGage Steam Chemical Integrator strips were placed inside 4 - 3 1/2" x 8" bags that were placed one on top of each other and then tape with autoclave tape to prevent the seal of the bags to be destroyed. In addition, 2 integrators were placed underneath the autoclave tape on the seal of the bags.

The SteriGage is a sophisticated chemical indicator that shows the effectiveness of a sterilization method (Steam at 121.1 degrees Celsius) for a specified time. It provides visual accept/reject readout to verify that the sterilant has penetrated to the point of placement in the load and confirms that sufficient exposure conditions have occurred.

Results:

This cycle demonstrated to be effective for sterilization of the 15 - 3 1/2" x 8" bags placed with the describe load of wrapped goods.

Recommended Action:

None

Conclusion:

VWR Oven located in storage room has been verified to be effective for depyrogenation at a chamber temperature of $\geq 250^{\circ}\text{C}$ for two hours

The autoclave in clean room 1 used by New England Compounding Center has been verified to be effective for sterilization of 15 - 3 1/2" x 8" bags.

Marvel Freezer temperature of -12°C to -27°C is suitable for drug substances used by NECC.

Written By: Alex Rodriguez

Date: 04-05-06

Reviewed By: James L. Latham

Date: 04-05-06

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April 2002 FDA Inspections Report

(FEI # 3003623877)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

One Montvale Avenue
Stoneham, MA 02180
(781) 596-7700 Facsimile (781) 596-7896

DATE(S) OF INSPECTION

04 / 9, 10, and 16 / 2002

FEI NUMBER

3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

To: Barry Cadden, R. Ph, Owner and Director of Pharmacy

FIRM NAME

New England Compounding Pharmacy, Inc.

STREET ADDRESS

697 Waverly Street

CITY, STATE AND ZIP CODE

Frammingham, MA 01702

TYPE OF ESTABLISHMENT INSPECTED

Compounding Pharmacy

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Betamethasone Repository Injection (Betamethasone Acetate and Betamethasone Sodium Phosphate Suspension 6 mg/ml), a product which is intended to be sterile, is sampled for sterility and endotoxin testing immediately after sterilization of the bulk compounded product in a 1000-ml beaker. Individual vials of Betamethasone Repository are not filled until the test results for sterility and endotoxin (pyrogen) are received from the contract testing laboratory, a process which can take up to one week after the sterilization and sampling of the bulk product have occurred. While laboratory test results are pending, the 1000-ml beaker and its contents are stored in the firm's laminar flow hood. The only other measure taken during this period to prevent recontamination of the bulk suspension is the use of a covering of multiple layers of aluminum foil over the mouth of the beaker.
2. The samples taken immediately after completion of the autoclave sterilization cycle (134° for 20 minutes) are not representative of product that remains in the original 1000-ml beaker for up to one week past the time of sampling.
3. The firm's validation of the autoclave cycle does not take into account the fact that the autoclaved bulk product is not transfilled into a final container/closure system (vials) for a period of up to one week.
4. On at least one occasion, a lot number (Lot 02 01 2002@027) was generated in the firm's computerized record keeping system, for which no associated records could be retrieved. It cannot be determined whether:
 - this lot was distributed and records covering its preparation were never created or are no longer in existence, or
 - the preparation of this lot never proceeded, but no record of its cancellation was entered in the record keeping system.

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Constance Desjardins, Investigator

Kristina M. Joyce, Investigator

Mark Lookabaugh, Compliance Officer

DATE ISSUED

04 / 16 / 2002

NEW ENGLAND COMPOUNDING PHARMACY INC.
697 WAVERLY STREET
FRAMINGHAM, MA 01702
E: 419.4140. 4/16/02

CDS/KJ/ML

PAGE 1

REASON FOR INSPECTION

This investigation was initiated from HFD-330, Division of Prescription Drug Compliance and Surveillance. HFD-330 requests follow-up of 2 MedWatch Adverse Event Reports. The assignment was entered into FACTS under ID #298826 as a domestic investigation to be conducted under PAC 56D015. The assignment also requests working jointly with the Mass Board of Pharmacy.

HISTORY

There is no previous investigational/inspectional history on file for New England Compounding (NEC) Pharmacy Inc., Framingham, MA 01702. The Mass Pharmacy Board has inspected NEC in the past.

SUMMARY OF FINDINGS

This investigation of New England Compounding Pharmacy Inc., Framingham, MA 01702 revealed that the subject lot, 02012002@27 identified in MedWatch Forms, could not be traced through NEC Pharmacy records. The owner of NEC, Barry Cadden, R.Ph could offer no definitive explanation/or records. According to Mr. Cadden lot #02012002@27 did not exist. A review of the compounding operations was accomplished and areas of concern regarding sterility were discussed. An FD-483 was issued regarding sterility issues and lack of lot accountability.

The Mass Board of Pharmacy performed their own independent inspection while the FDA investigation was in progress.

Note: Mass Board of Pharmacy was invited to participate by the FDA NWE-DO, per Headquarters' assignment.

PERSONS INTERVIEWED/AREAS OF RESPONSIBILITY

On 4/9/02 credentials were displayed and a Notice of Inspection was issued to Barry J. Cadden R.Ph, Owner & Director of the Pharmacy.

Mr. Cadden coordinated all the information for this report. Mr. Cadden is the Owner of NEC. He identified his wife Lisa Cadden R.Ph as Vice President of NEC. Mrs. Cadden was introduced on the second day of the inspection.

NEW ENGLAND COMPOUNDING PHARMACY INC.
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EI 4/9, 4/10, 4/16/02

CDS/KJ/ML

PAGE 2

Mr. Cadden was informed that the purpose for the inspection was a follow-up to adverse events involving the compounded product Betamethasone acetate/betamethasone sodium phosphate. (The drug was administered via an epidural injection in the adverse event reports.) Note: Per instruction from HFD-330, detailed information such as lot number & MedWatch Reporter was not shared with Mr. Cadden for confidentiality reasons.)

Mr. Cadden stated there are 8 employees, three of whom are involved in compounding. Mr. Cadden is the only individual that compounds sterile product. NEC has been in business about 4 years.

On the first day of inspection, Mr. Cadden was cooperative & supplied some documents. The second day of inspection, Mr. Cadden had a complete change in attitude & basically would not provide any additional information either by responding to questions or providing records. Mr. Cadden challenged FDA jurisdiction/authority to be at his pharmacy. He indicated he had consulted with his lawyer. From that point on it was essentially "talk to my lawyer".

JURSDICTION

Section 704(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act describes the nature of FDA inspectional authority with regard to retail pharmacies. In particular, this section states that the "provisions of the second sentence of paragraph (1) shall not apply" to pharmacies operating in the retail capacity. The sentence being referred to is contained in Section 704(a)(1)(B). It provides the authority during factory inspections of firms that manufacture, process, pack, or hold prescription and nonprescription human drugs, an (restricted) devices for access to "records, files, papers, processes, controls, and facilities" bearing on whether these products are in violation of the Act. In summary, our inspectional authority at pharmacies operating in a retail capacity consists of being able to:

- enter, at reasonable times (Section 704(a)(1)(A), and
- inspect, at reasonable times, and within reasonable limits and in a reasonable manner (Section 704(a)(1)(b), the establishment and its equipment and operations

However, the owner of the pharmacy is not obligated to furnish records, as is normally the case when a facility that processes drug products is being inspected.

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On the first day of the inspection (April 9) we were allowed to review and were furnished with copies of records related to the compounding of Betamethasone Repository Injection. Later the same day, Mr. Cadden raised as an issue the precise nature of FDA's authority to inspect retail pharmacies. However, at this time he did not express any reservations about having allowed us to review any of these records.

However, it became clear upon our return on the following morning, that Mr. Cadden had reconsidered this matter. He presented us with a printed copy of Title 21 of the United States Code, Section 374 (the codified version of Section 704 of the Act) that he had apparently downloaded from the Internet (www4.law.cornell.edu/uscode/21/374.html), with paragraph (2)(A) of Section 374 highlighted. Mr. Cadden stated that he was no longer willing to provide us with any additional records, unless we would identify the specific lot of Betamethasone Repository Injection that was the focus of this investigation. Since we had been specifically directed by CSO Richman (CDER/OC/Division of Prescription Drug Compliance and Surveillance) not to divulge this lot number, we were not in a position to comply with Mr. Cadden's request. From this point on, no additional records were provided or collected.

MEDWATCH ADVERSE EVENTS

Per HFD-330 Assignment, 2 Adverse Events, reported through the MedWatch system were identified to the NWE-DO for follow-up. The information contained in these reports were not openly shared with NEC nor with Mass Board of Pharmacy. Both MedWatch reports were from the same Reporter and involved the same lot number of Betamethasone.

Note: An inspection/subsequent action of a California Compounding Pharmacy for Betamethasone was revealed during a telecon with HFD-330 while the NEC investigation was in progress. (The information was not included with the NWE-DO assignment.) Very similar operational problems existed with the California Compounding Pharmacy that were encountered with NEC. The action for the California Compounding Pharmacy was taken by the State Pharmacy Board. See Attachments to this report for the FD-483 and State Board of Pharmacy, California Case #2427 Accusation.

The NWE-DO FDA Investigators conducted the NEC MedWatch follow-up investigation by requesting a printout of the Betamethasone Compounded Product for the year 2002. The subject lot number was listed on this printout, i.e., lot #02012002@27. See Exhibit #1 for this printout.

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From this printout, lot #'s 02152002@10 and 02012002@27 were selected for review. Formula Worksheets for lot #02152002@10 were provided, see Exhibit #2. No records for lot #02012002@27, (the MedWatch lot number), were provided. Mr. Cadden indicated that there were no Compounding records for this lot. When he accessed the database, the only document generated was a Prescription log with a "date made", of 2/1/02 for 1000 ml. See Exhibit #3.

Mr. Cadden expressed his belief that the Betamethasone was never compounded under lot #02012002@27. However he could not provide any documents to support his belief, such as a cancelled lot etc.

Due to MedWatch confidentiality restrictions, the status of the subject lot could not be pursued via this avenue.

Note: Complaint files are not maintained per se. Mr. Cadden stated that complaints are kept within a Customer file. FDA could not reveal the Complainant to Mr. Cadden.

The FDA Investigators then contacted the MedWatch Reporter in an attempt to verify the existence of lot #02012002@27. The Reporter, (b) (6), (b) (7)(C) was contacted by phone. The contact person was identified to FDA as (b) (6), (b) (7)(C).

(b) (6), (b) (7) stated that a total of probably 5 incidents occurred after using subject Betamethasone on patients. The two more recent incidents were reported via MedWatch. Refer to MedWatch Reports for details. They are Assignment Attachments to this report.

(b) (6), (b) (7) said he had no product remaining, all had been returned to NEC. He stated that he spoke to 'Barry' by phone describing the incidents but did not tell him he was reporting adverse events on MedWatch Forms.

(b) (6), (b) (7) reviewed his paperwork, including PO Invoice, Return Goods, but could not find any paperwork specifically identifying the subject lot.

(b) (6), (b) (7) stated he would provide copies of these documents to the FDA NWE-DO. They were faxed the same day and hard copies would be mailed overnight. See Attachments for these records. Note: There is no lot number identified on any of the records provided by (b) (6), (b) (7) (C)

was asked specifically if FDA could share the MedWatch Reports with Mr. Cadden. (b) (6), (b) (7) (C) said he would not want the information shared.

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Note: A follow-up assignment at the
considered if HFD-330 deems it appropriate.

(b) (6), (b) (7)(C) location should be

Due to jurisdiction/confidentiality restrictions, this FDA investigation could not proceed to any definitive resolution of issues raised in the Headquarter's assignment. HFD-330 Assignment contacts, Fred Richman and Kathy Anderson were fully informed of problems/barriers that were encountered throughout the inspection. NWE-DO Compliance Director, David Elder and NWE-DO Drug SI, Ellen Madigan were also made aware of the situation.

Prior to concluding the investigation, poor practices and areas of concern were discussed via Conference Call with HFD-330 and NWE-DO Management. The FDA Investigators were encouraged to issue an FD-483 to NEC.

The FDA Investigators impressed upon HFD-330 and NWE-DO Management that due to limitations on information gathering and access to records, the FD-483 observations could not/would not be supported with documentation. The FDA Investigators were directed to issue the 483 (even in light of the lack of documentation).

The FD-483 was faxed to HFD-330 for review and comment prior to issuance. Fred Richman and Kathy Anderson deleted 3 of the 7 Observations and modified one observation, (#5) by removing the lot number identification.

A conference call involving NWE-DO Investigators, HFD-330 Fred Richman, Kathy Anderson and CDER FOI Specialists Andrea Mascialea and Roy Castle was held on 4/15/02. FOI Specialists had no problem including the lot number on the observation. This was based on the fact that the suspect lot number was never revealed to NEC as the suspect lot number on the MedWatch Form.

The modified 483 was issued on 4/16/02 with 4 observations listed. Numbers 1-3 involved sterility issues. Observation 4 essentially described lack of lot number accountability. Refer to List of Observations for details, an attachment to this report.

OPERATIONS

The firm is a compounding pharmacy. The hours of operation are Monday through Friday 9 am to 5 pm. All information was obtained from Mr. and Mrs. Cadden. There are 8 employees total, including 2 Registered Pharmacists, 1 data entry, 2 secretarial staff, and 3 pharmacy technicians. Pharmacists and Technicians receive Compounding Technique Certification (30 hours) from Professional Compounding Centers of America (PCCA, Houston, Texas).

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Formulations for compounding are obtained from PCCA. The firm's prescription software (PK Software) is from PCCA. Raw materials are obtained primarily from PCCA, with alternate source Spectrum (New Brunswick, NJ). Certificates of Analysis are provided with Spectrum products. COA's were provided with PCCA products on request. See Exhibit #'s 4(a-b) for representative examples. Sterile compound product samples are sent to Analytical Research Labs (Oklahoma City, OK) for sterility and endotoxin testing.

Medications are compounded pursuant to written/telephone/fax prescriptions from physicians/licensed facilities. The firm deals directly with patients, physicians and institutions. The firm states they fill patient specific prescriptions only, and that they have no wholesale functions. See Exhibit #5 for a representative Order Form. Mr. Cadden states that he is the only employee who compounds sterile products.

Leslie Doyle, R.Ph, from the Massachusetts Board of Pharmacy conducted her own independent audit on the second FDA on-site inspection of 4/10. Ms. Doyle was made aware of our concerns/findings regarding the Betamethasone Repository 6mg/ml injectable. Investigator Joyce accompanied Ms. Doyle for a State general inspection. Additional findings included:

- 1) Absence of DEA license on premises
- 2) Absence of DEA Class II Narcotic inventory on premises
- 3) Medication refrigerator contained employee beverages
- 4) Medications (ketoprofen, specifically) are commonly transferred from large bulk container to smaller (ketoprofen) container for ease of dispensing (therefore medication would be transferred to smaller container with incorrect lot and expiration date).
- 5) No reverse distributor for disposal of unused/unacceptable materials

The firm compounds betamethasone product both with (multi-dose vial) and without (single dose vial) preservative. Limited information about the compounding process was obtained. Mr. Cadden states he uses a Log Formulation Worksheet (LFW) (Exhibit #2) which outlines the steps taken in compounding the betamethasone. We were denied a copy of the PCCA formulation used to derive the Log Formulation Worksheet (LFW). A copy of the firm's "Policies & Procedures for Compounding Sterile Products" was obtained (Exhibit #6). The medication name on this document is "hyaluronidase", but Mr. Cadden claims this document applies to all sterile products. It outlines controls for the facility, equipment, maintenance, personnel, quality assurance/control, and dispensing. The lot in question from the MedWatch reports was lot #02012002@27, which contained preservative according to firm records. See Exhibit #1 for lot number printout.

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Mr. Cadden states when compounding the product, he accesses the LFW in the computer. The computer assigns a lot number based on the date and order of compounding (i.e.: 02012002@27 would've been the 27th item entered in the computer for compounding on February 1, 2002). He then determines the quantity to compound and prints the LFW. The product is made according to the quantities and directions on the LFW. The location where raw materials are mixed is unclear. Mr. Cadden stated that he then covered the mixture in the beaker with aluminum foil and placed it in the autoclave for 20 minutes at 134° (the autoclave is located outside of the clean room). Then he brings the compound to room temperature in the beaker on the magnetic stirrer (2-4 hours) due to the suspending agent. He then takes suspension from the beaker and transfers it to vials. The vials are labeled with self made computer labels. See Exhibit #7 for a representative example of a label. A sample is sent to ARL for sterility and endotoxin testing. Mr. Cadden states he waits for acceptable lab results before dispensing product.

Mr. Cadden stated on/about 3/19/02 through 4/6/02 he received ARL results positive for endotoxin (greater than 100 ppb). See Exhibit #'s 8(a-d) for Test Results. He stated these lots (about 4 lots total) were awaiting disposal at his facility. After research, Mr. Cadden decided to change the suspending agent carboxy methylcellulose to polyglycol. After making a lot on 4/6/02, Mr. Cadden stated he sent his samples to ARL, then left the product beaker covered with aluminum foil on the magnetic stirrer in the hood awaiting lab results. Mr. Cadden told us it could take anywhere from seven to ten days to obtain lab results. This beaker was observed in the laminar flow hood on 4/9/02. When questioned about this practice, Mr. Cadden stated he didn't want to waste the money on vials or the effort in transfilling the vials if the 4/6/02 lot failed testing. He stated he would transfill the vials upon receiving satisfactory lab results. It was discussed with Mr. Cadden that this was not an acceptable process for maintaining product sterility. Upon returning to the firm 4/10/02, the hood was clean and Mr. Cadden was asked the whereabouts of the 4/6/02 lot. He stated he received negative lab results the night before and had transfilled the lot into vials that morning. He accredited the positive endotoxins to the previous suspending agent. When asked if he had intentions of dispensing the lot, he said yes. The FDA investigator suggested to Mr. Cadden that he retest the 4/6/02 lot again after transfilling the vials since the product sat in a beaker for 5 days before transfilling into vials. The risks and impacts of non-sterile product to patients and his firm were discussed. Mr. Cadden agreed to retest the lot to confirm sterility and lack of endotoxins.

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AREAS OF CONCERN

- 1) No accessible system for retrieving complaints/ADR reports. The firm claims that these documents are filed under patients or institutions, so they cannot be retrieved without that specific information. This prohibits the firm from identifying and tracking problems with individual medications or lot numbers.
- 2) Beyond use dating not substantiated. Preservative and Preservative Free product both receive the same expiration date of six months. There is no indication as to why/how this date was chosen and if laboratory data confirms these expiration dates.
- 3) Preservative vs. preservative free: The only label differentiation between the two is "***MDV***" and "PF".
- 4) Batch formula worksheets contain expired products. Mr. Cadden states they use in date materials, but probably have not updated their computer with correct lot numbers and dates. If raw materials were to be recalled, the firm would have trouble recalling their correct products since it is not apparent what lots are used for compounding medications.
- 5) Recordkeeping poor; lot numbers exist with no prescriptions linked as being dispensed. This would again prohibit timely recall of product to patients.
- 6) Positive endotoxin source still definitively unknown.
- 7) Non-sterile laminar flow hood environment: On the first day of the investigation, the clean room was observed. The laminar flow hood contained a beaker covered with aluminum foil on a magnetic stirrer. To the left of the beaker sat two-three bags of vial caps. To the right of the beaker sat a plastic (Rubbermaid-like) tray with miscellaneous items. When asked about this practice, Mr. Cadden acknowledged that there were unsterile items placed in the hood, but that he tried to wipe them down with alcohol before placing them inside the hood.
- 8) Autoclave: there is no SOP in place for use of or maintenance of the autoclave. Mrs. Cadden says the machine is "cleaned/flushed" weekly on Friday night. There is no documentation to support this statement, which was also noted by the state representative.

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ASSIGNMENT QUESTIONS

The following represents information gathered to address specific questions included in the assignment. (Refer to the Assignment for the list of questions.) The information is supplied in the same sequence as the questions are asked in the assignment.

- #1 This question is to be answered by the Mass Board of Pharmacy.
- #2 yes
- #3
 - they sometimes have a week's worth of product on hand
 - 1000 ml compounded
 - dispension timeframe varies
- #4 no, supposedly they do not sell wholesale
- #5
 - they do not dispense directly to patients
 - yes, they provide to institutional pharmacy for dispensing to patients
- #6
 - they dispense 200/300 Rx's per month
 - about 50% out of state
- #7 see EIR
- #8 not provided
- #9 refer to EIR, some COA's on file
- #10 no formal written complaint system
Supposedly complaints are kept within a Customer File.

DISCUSSION WITH MANAGEMENT

At the conclusion of inspection, an FD-483 List of Observations was issued to Barry J. Cadden, R.Ph, Director of Pharmacy & Owner of NEC. Also present was Beverly Gilroy, Administrative Assistant. Ms. Gilroy was present on 4/10/02 and at the closing on 4/16/02. Essentially Ms. Gilroy's presence was as 'note taker'.

All 3 FDA Investigators were present. The Observations included:

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Observation #1 Betamethasone Repository Injection (Betamethasone Acetate and Betamethasone Sodium Phosphate Suspension 6 mg/ml, a product which is intended to be sterile, is sampled for sterility and endotoxin testing immediately after sterilization of the bulk compounded product in 1000-ml beaker. Individual vials of Betamethasone Repository are not filled until the test results for sterility and endotoxin (pyrogen) are received from the contract testing laboratory, a process which can take up to one week after the sterilization and sampling of the bulk product have occurred. While laboratory test results are pending, the 1000-ml beaker and its contents are stored in the firm's laminar flow hood. The only other measure taken during this period to prevent recontamination of the bulk suspension is the use of a covering of multiple layers of aluminium foil over the mouth of the beaker.

In response to item #1, Mr. Cadden stated it was not his usual practice to wait for up to one week before filling individual vials. He stated the practice of transfilling the vials normally occurs within a few hours after autoclaving, once cooling of the beaker with product mixture is complete. He stated the delay (of up to one week) in transfilling only occurred during the period in which product samples were testing positive for endotoxin, and it was for that reason he did not want to transfill the vials unless the sample received satisfactory laboratory analysis. It was explained to Mr. Cadden that these observations were discussed with him during the investigation, but Mr. Cadden declined to provide documentation showing this was not his normal practice. Mr. Cadden also stated that the beaker with product witnessed by FDA investigators actually didn't contain the betamethasone repository. Mr. Cadden was reminded of the contradictory information he provided to the investigators during the investigation.

Observation #2 The samples taken immediately after completion of the autoclave sterilization cycle (134° for 20 minutes) are not representative of product that remains in the original 1000-ml beaker for up to one week past the time of sampling.

In response to item #2, Mr. Cadden stated it was incorrect because item #1 was incorrect per above.

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Observation #3 The firm's validation of the autoclave cycle does not take into account the fact that the autoclaved bulk product is not transfilled into a final container/closure system (vials) for a period of up to one week.

In response to item #3, Mr. Cadden stated it was incorrect because item #1 was incorrect per above.

Observation #4 On at least one occasion, a lot number (Lot 02012002@27) was generated in the firm's computerized recordkeeping system, for which no associated records could be retrieved. It cannot be determined whether:

- this lot was distributed and records covering its preparation were never created or are no longer in existence, or
- the preparation of this lot never proceeded, but no record of its cancellation was entered into the recordkeeping system

See Exhibit #'s 1 and 3 to support this observation.

In response to item #4, Mr. Cadden stated he agreed with this observation. He also stated that of the two possibilities, he agreed with the latter the most.

Mr. Cadden indicated he would consider a written response to the 483 Observations but was basically non-committal.

The inspection was concluded.

This investigative report was prepared by all 3 FDA Consumer Safety Officers. Primary responsibility for Headings included:

- C. DeSimone CSO, MedWatch Section
- K. Joyce, CSO, Operations Section
- M. Lookabaugh, Compliance Officer, Jurisdiction Section

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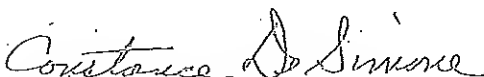
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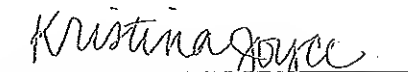
EXHIBITS

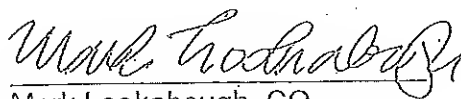
- #1 2002 Betamethasone lot number Printout
- #2 Representative Formula Worksheet
- #3 Prescription Log, 1 page
- #4 Certificates of Analysis
 - (a) Spectrum
 - (b) PCCA
- #5 Representative Order Form
- #6 Policies & Procedures, Sterile Products
- #7 Representative Vial label
- #8 ARL Results
 - (a) #21119 (c) #21178
 - (b) #21162 (d) #21179

ATTACHMENTS

FD-482 Notice of Inspection
FD-483 List of Observations
FACTS Assignment ID #298826
HFD-330 Assignment dated 4/4/02
HFD-330 FAX dated 4/9/02, 18 pages
Related MedWatch Information sent to NWE-DO from Reporter


Constance DeSimone, CSO
US FDA NWE-DO


Kristina Joyce, CSO
US FDA NWE-DO


Mark Lookabaugh, CO
US FDA NWE-DO

CDS/KJ/ML/cj;4/19,22,23,24/02

a:/NECPI.EIR

Distribution:

O: EIR, Exhibits, Attachments to New England Compounding Pharmacy
FEI 3003623877
cc: EIR, Exhibits, Attachments to HFD-330, Attn: E. Richman
cc: EIR only, Compliance Branch, Attn: M. Lookabaugh NWE-DO

October 2002-February 2003 FDA Inspections Report

(FEI # 3003623877)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

One Montreal Avenue, 4th Floor

Stoughton, MA 02180

(781) 596-7700

DATE(S) OF INSPECTION

10/28, 12/12 & 14/02, 1/14-15/03, 2/16/03

FBI NUMBER

2033073877

NAME AND TITLE OF THE INSPECTOR(S) VISITING

TO: Barry J. Cadden, Director of Pharmacy

FIRM NAME

New England Compounding Center

STREET ADDRESS

697 Waverly Street

CITY, STATE AND ZIP CODE

Framingham, MA 01702

TYPE OF ESTABLISHMENT INSPECTED

Pharmacy

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

The below observations pertain to drug products that personnel prepare at your firm for which you claim are sterile (for example, injections) and are prepared in anticipation of a prescription.

J. For the preparation of sterile drug products distributed by your firm (such as those intended for injection), there is no adequate documentation available to verify that they meet set standards (such as specifications and/or USP limits if applicable) at the time they are distributed or for the shelf life (expiration dating period) of these products. This includes the absence of documentation to verify the following:

- A. Personnel performing preparation steps are not contaminating the finished products.
- B. Workspaces are cleaned and sanitized to prevent product contamination.
- C. Equipment and supplies entering the product preparation area are decontaminated/cleaned to prevent product contamination.
- D. The environment in the area where the filling and closing operations are performed is adequate to prevent product contamination (this includes the lack of documentation pertaining to environmental monitoring in the immediate area while product is exposed to the environment, such as during filling and prior to container closure).
- E. All autoclave sterilization processes are suitable for the sterilization of drug product preparation equipment and components (which includes vial stoppers and bulk product). Some examples are:
 - a. Lack of documentation to verify that all critical processing parameters and procedures being used are appropriate in ensuring that final products meet all standards (such as sterility); this includes, sterilization time, temperature, size and nature of load, and chamber loading configuration.
 - b. Records do not state the actual critical parameters used during processing.
 - c. Lack of documentation to verify that the autoclave itself is maintained and calibrated to perform its intended function.
 - d. The autoclave process used on bulk drug products does not have an effect on stability or product specifications.

F. The transfer of bulk drug product and equipment from the autoclave (after it went through an autoclave process) from one room to another room in which further preparation steps are performed in a laminar air flow workbench, is not introducing contamination into the finished product.

G. All components, including drug substances, vials, and rubber stoppers, meet set standards making them suitable for their intended use. This includes that components and process water are not contaminating finished products.

H. Equipment used to measure the amount of ingredients/components are calibrated and maintained to perform their intended function.

I. Testing procedures and sampling procedures being performed for all drug products are representative of the lots/batches being tested.

J. That for each preparation of a sterile product or batch of sterile products, there has been appropriate laboratory determination of conformity with purity, strength, sterility, and non-pyrogenicity, in accordance with established written specifications and policies.

K. Preparation steps are being performed in a correct manner since batch record preparation instructions are lacking significant preparation steps, which includes mixing procedures.

L. Final containers are capable of maintaining product integrity (i.e. identity, strength, quality, and purity) throughout

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE

Daryl A. Dewoskin
Kristina M. Joyce

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Daryl A. Dewoskin, CSO
Kristina M. Joyce, CSO

DATE ISSUED

2/10/03
2/10/03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
One Montvale Avenue, 4th Floor
Stonham, MA 02180
(781) 596-7700

DATE(S) OF INSPECTION
10/24, 12/12&18/02, 1/14-15/03, 2/10/03

FEI NUMBER
3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS REQUESTED

TO: Barry J. Cadden, Director of Pharmacy

FIRM NAME
New England Compounding Center

STREET ADDRESS
697 Waverly Street

CITY, STATE AND ZIP CODE
Framingham, MA 01702

TYPE OF ESTABLISHMENT INSPECTED
Pharmacy

the shelf life of the product.

M. All drug products prepared and packaged at your site meet specifications and USP limits (if applicable) for the expiration dating period assigned. According to documentation and your statements, all drug products are assigned an expiration date of 60 days if they do not contain a preservative, three months if they are not filtered, and 6 months if they are filtered. No data was available for any of your products prepared at your firm to support these expiration date periods.

In addition, for all of the items above there were no written procedures available pertaining to the performance of these duties and processes.

2. There are no written procedures pertaining to the handling of complaints, nor does your firm maintain a complaint file.

3. There was no documentation available for the handling and disposition of reports of patient problems, complaints, adverse drug reactions, drug product or device defects, and other adverse events reported. For example, after a medical facility reported adverse events associated with lot 05312002@16, your firm conducted a recall of injectable steroid products and implemented shorter expiration dates and use of pre-sterilized vials. You stated you have no documentation available pertaining to an investigation being performed for this and other related lots which shows that adequate follow-up action was taken.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Daryl A. Dewar</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Daryl A. Dewar, CSO	DATE ISSUED 2/10/03
	<i>Kristina M. Joyce</i>	Kristina M. Joyce, CSO	2/10/03
INSPECTIONAL OBSERVATIONS			

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

Food and Drug Administration Establishment Inspection Report

Date Assigned: 12/17/2002 Inspection Start Date: 10/24/2002 Inspection End Date: 02/10/2003
 Firm Name & Address: New England Compounding Center, 697 Waverly Street Framingham, MA 01720 US
 Firm Mailing Address:
 FEI: 3003623877 JD/TA: 13 County: MIDDLESEX Est Size: 0 - 24,999
 Phone: (508)820-0606 District: NWE-DO Profiled: No
 Conveyance Type: % Interstate: Inspectional Responsibility:

Endorsement

SUMMARY: This inspection covered the firm's compounding processes for sterile injectable steroid products which included the following: methylprednisolone acetate and betamethasone repository (betamethasone sodium phosphate and betamethasone acetate). The MABP accompanied us during most of the inspection at the request of HFM-330. The current inspection involved sampling of NECC products from within the New York and New England District areas. Sample results revealed that the firm has sterility and potency issues with injectable steroid suspensions (betamethasone repository USP and methylprednisolone acetate USP).

On 2/10/03, at the close of this inspection, an FDA-483, Inspectional Observations, was issued to Barry Cadden, R.Ph. The FDA 483 Observations pertained to the following: 1) inadequate documentation to verify sterile drug products distributed meet set standards (such as specifications and/or USP limits if applicable) or the assigned shelf life, 2) failure to maintain complaint files, including written procedures pertaining to the handling of complaints, and 3) lack of documentation for the reported adverse events associated with lot 05312002@16 of methylprednisolone acetate which includes handling and disposition of reports of patient problems, complaints, adverse drug reactions, and drug product or device defects.

(SEE CONTINUATION SHEET for Reason for Inspection, History, and Voluntary Corrections)

CLASSIFICATION: OAI; referral to Massachusetts State Board of Pharmacy. Recommend firm be prohibited from manufacturing until they can demonstrate ability to make product reproducibly and dependably. If state is unwilling to take action, recommend firm be enjoined for GMP deficiencies.

DISTRIBUTION:

Orig: CF
 C/S & EIR: FMD-145, MA Bd Pharm thru Compl Br for FOI clearance
 C/S & 483: WSB, Souza
 CC (C/S, EIR, 483, EXH & ATTCH): MCL, HFM-330 (Kathy Anderson)

Endorsement Location: NWE-DO CF

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
Kristina M Joyce	03/07/2003 06:49 AM ET	William S Boivin	03/07/2003 05:36 PM ET
Kristina M Joyce	03/07/2003 06:49 AM ET	William S Boivin	03/07/2003 05:30 PM ET
Kristina M Joyce	03/06/2003 01:08 PM ET		ET
Kristina M Joyce	03/06/2003 12:46 PM ET		ET
Kristina M Joyce	03/06/2003 08:46 AM ET		ET
Kristina M Joyce	03/05/2003 02:50 PM ET		ET

Food and Drug Administration Establishment Inspection Report

FEI: 3003623877

Inspection Start Date: 10/24/2002

Inspection End Date: 02/10/2003

Firm Name & Address:

New England Compounding Center, 697 Waverly Street Framingham, MA 01720 US

Related Firm FEI:

Name & Address of Related Firm:

Registration Type

There are no Registration Types

Registration Dates

Establishment Type

M Manufacturer

M Manufacturer

District Use Code:

Industry Code

60 Human and Animal Drugs

64 Human and Animal Drugs

Food and Drug Administration Establishment Inspection Report

FEI: 3003623877

Inspection Start Date: 10/24/2002

Inspection End Date: 02/10/2003

Firm Name & Address: New England Compounding Center, 697 Waverly Street Framingham, MA 01720 US

Inspection Basis: Surveillance

Inspected Processes & District Decisions

PAC Establishment Type
56D015 Manufacturer

Products/
Process
64 L C K

MQSA Reschedule Re-Inspection
Insp Date Priority
Surveillance

Inspection
Conclusions
Correction Indicated (CI)

Final District
Decision? Decision Date District Decision Type
Y 03/07/2003 Referred to State (RTS)

District Decision
Made By
Boivin, William S

Org Name
NWE-DRUGS

Remarks:

PAC Establishment Type
56002 Manufacturer

Products/
Process
64 L C K

MQSA Reschedule Re-Inspection
Insp Date Priority
Surveillance

Inspection
Conclusions
Correction Indicated (CI)

Final District
Decision? Decision Date District Decision Type
Y 03/07/2003 Referred to State (RTS)

District Decision
Made By
Boivin, William S

Org Name
NWE-DRUGS

Remarks:

Food and Drug Administration Establishment Inspection Report

FBI: 3003623877

Inspection Start Date: 10/24/2002

Inspection End Date: 02/10/2003

Firm Name & Address: New England Compounding Center, 697 Waverly Street Framingham, MA 01720 US

Products Covered

Product Code	Est Type	Description	Additional Product Description
64 L C K 07	Manufacturer	Betamethasone Sodium Phosphate (Glucocorticoid); Human Rx/Single Ingredient; Sterile Liquid	in amber vial
64 L C K 45	Manufacturer	Methylprednisolone Acetate (Glucocorticoid); Human Rx/Single Ingredient; Sterile Liquid	in amber vial

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
Joyce, Kristina M	INV	NWE-DO	56D015	Manufacturer	64 L C K	200
Dewoskin, Daryl A	INV	NWE-DO	56D015	Manufacturer	64 L C K	35
Joyce, Kristina M	INV	NWE-DO	56002	Manufacturer	64 L C K	20
Dewoskin, Daryl A	INV	NWE-DO	56002	Manufacturer	64 L C K	15
Total Hours:						270

Food and Drug Administration Establishment Inspection Report

FEI: 3003623877

Inspection Start Date: 10/24/2002

Inspection End Date: 02/10/2003

Firm Name & Address: New England Compounding Center, 697 Waverly Street Framingham, MA 01720 US

Inspection Result

Trips Num

EIR Location
NWE-DO CF

Inspection Summary

REASON FOR INSPECTION: The investigation of New England Compounding Center (NECC) was conducted in response to an assignment (dated 8/2/02) received from HFM-330, Office of Compliance, Division of Prescription Drug Compliance and Surveillance, Center for Drug Evaluation and Research. The investigation was done in accordance with HFM-330 assignment/guidance and CPG 460.200 (Pharmacy Compounding). A limited inspection was performed which included covering aseptic processing procedures used at NECC. Sections of the current USP were used as a reference. FACTS #332851.

The initial assignment requested an investigation to obtain information regarding three MedWatch reports associated with the use of methylprednisolone acetate preservative free 80mg/ml that was compounded by NECC in May of 2002. Per supervisory request, this assignment was changed to conduct an inspection during December 2002. The HFM-330 assignment requested answers to the following questions: 1) have any other patients experienced adverse events from the compounded product and 2) has the pharmacy conducted follow up to determine whether there is a problem with the compounded product.

HISTORY: The last FDA inspection of NECC was in April 2002. The inspection was classified VAI and a FDA-483 (List of Observations) was issued to Mr. Cadden citing sterility issues and lack of lot accountability. The practices that were cited on the previous FDA 483 were not in place and therefore the correction of these items was not an issue.

VOLUNTARY CORRECTIONS: n/a

Food and Drug Administration Establishment Inspection Report

FBI: 3003623877

Inspection Start Date: 10/24/2002

Inspection End Date: 02/10/2003

Firm Name & Address: New England Compounding Center , 697 Waverly Street Framingham, MA 01720 US

IB Suggested Actions

Action	Remarks
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Referrals

Org Name	Mail Code	Remarks
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Refusals

Inspection Refusals:

Samples Collected

Recall Numbers

Related Complaints

Sample Number

Recall Number

Consumer Complaint Number

167876

167877

169126

169127

169128

169129

169130

169131

169132

169133

208553

FDA 483 Responses

483 Issued?: Y 483 Location: NWE-DO CF

Response Type	Response Mode	Response Date	Response Summary
Further review needed	Letter	02/26/2003	Response outlined corrective actions; referred to MA State Bd of Pharmacy.

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FACTS #332851
KMJ/DAD

FEI# 3003623877
EI Start: 10/24/02
EI End: 2/10/03

SUMMARY

The investigation of New England Compounding Center (NECC) was conducted in response to an assignment (dated 8/2/02) received from HFM-330, Office of Compliance, Division of Prescription Drug Compliance and Surveillance, Center for Drug Evaluation and Research. The investigation was done in accordance with HFM-330 assignment/guidance and CPG 460.200 (Pharmacy Compounding). A limited inspection was performed which included covering aseptic processing procedures used at NECC. Sections of the current USP were used as a reference.

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On 10/24/02, Investigator Joyce showed credentials, and issued an FDA 482, Notice of Inspection (including the attachment Resources for FDA Regulated Businesses), to Barry J. Cadden, Owner and Director of Pharmacy. On 10/24/02 Inv. Joyce was accompanied by Leslie Doyle of the Massachusetts Board of Pharmacy (MABP). On 12/12/02 FDA Credentials were shown, and a second FDA 482 was issued to Mr. Cadden by Investigators Joyce and DeWoskin. On 12/12/02 Inv. Joyce and DeWoskin were accompanied by James Emery, Investigator, and Arthur Chaput, Quality Assurance Surveyor, from the MABP. On 12/18/02 Investigators Joyce and DeWoskin returned to the firm accompanied by Mr. Emery. On 1/14/03 Inv. DeWoskin showed credentials, and issued an FDA 482 to Mr. Cadden for the purpose of sample collection. On 1/15/03 Inv. DeWoskin showed credentials, and issued another FDA 482 to Beverly Gilroy, Educational Coordinator, for the purpose of picking up a sample of vial caps. On 2/10/03 Inv. Joyce and Inv. DeWoskin showed credentials, and they issued another FDA 482, since they had not been at the firm for about three weeks.

This inspection covered the firm's compounding processes for sterile injectable steroid products which included the following: methylprednisolone acetate and betamethasone repository (betamethasone sodium phosphate and betamethasone acetate). The MABP accompanied us during most of the inspection at the request of HFM-330.

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The current inspection involved sampling of NECC products from within the New York and New England District areas. Sample results revealed that the firm has potency issues with injectable steroid suspensions (betamethasone repository USP and methylprednisolone acetate USP).

On 2/10/03, at the close of this inspection, an FDA-483, Inspectional Observations, was issued to Barry Cadden, R.Ph. The FDA 483 Observations pertained to the following: 1) inadequate documentation to verify sterile drug products distributed meet set standards (such as specifications and/or USP limits if applicable) or the assigned shelf life, 2) failure to maintain complaint files, including written procedures pertaining to the handling of complaints, and 3) lack of documentation for the reported adverse events associated with lot 05312002@16 of methylprednisolone acetate which includes handling and disposition of reports of patient problems, complaints, adverse drug reactions, and drug product or device defects.

ADMINISTRATIVE DATA

Post inspection correspondence should be sent to Barry Cadden R.Ph., Director of Pharmacy, at the below address.

Inspected Firm:	New England Compounding Center
Location:	697 Waverly Street Framingham, MA 01702
Phone:	508-820-0606, 800-994-6322
FAX:	508-820-1616
Mailing Address:	697 Waverly Street Framingham, MA 01702

Dates of Inspection:	10/24/02, 12/12&18/02, 1/14-15/02, 2/10/03
Days in the Facility:	6
Participants:	Kristina M. Joyce, Investigator Daryl A. Dewoskin, Investigator

The BIR was written by Inv. Joyce and reviewed by Inv. Dewoskin.

FIRM INFORMATION

Pertaining to key firm personnel and their responsibilities no significant changes were made since the previous April 2002 inspection (see April 2002 BIR).

NECC holds a restricted license in the state of Massachusetts to operate as a compounding pharmacy. Essentially, MABP permits NECC to dispense only compounded pharmaceutical products. This is the second joint FDA and MABP investigation of the firm; the first was in April 2002 and was also a CDER assignment initiated by MedWatch complaints about the firm's betamethasone repository injectable.

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product. Please refer to the April 2002 EIR for the firm's hours and organizational structure. The MABP was present during the April 2002 investigation at the request of the FDA NWE-DO office per HFM-330 assignment.

On April 16, 2002 an FDA-483 was issued to Mr. Cadden citing sterility issues pertaining to the transfilling practices for betamethasone repository injection. Lot accountability was also cited for incomplete computerized record keeping of generated lot numbers. Mr. Cadden stated there is no lag in the transfilling time as noted in the 4/16/02 FDA-483. We were unable to verify this since compounding was not observed during this inspection. This inspection was classified VAI. No regulatory activities occurred as a result of the April 2002 inspection.

Since the April 2002 inspection, there have been significant changes to NECC's operations. One change is the acquisition of space previously occupied by a neighboring store. This space approximately doubled the firm's square footage which is currently being used for office space and a reception area. Mr. Cadden stated he now employs approximately twelve people in the following roles: 2 Pharmacists, 4 Pharmacy Technicians, 1 Bookkeeper, 2 Customer Service, 1 Receptionist and 2 Salespeople. He stated that the firm's employees make calls to out-of-state physicians and medical facilities and also maintain a web site.

Another change since the April 2002 inspection is the renovation of a previous reception area to accommodate the firm's new Class 10 hood. At the FDA inspectional closeout on 2/10/03, it was confirmed that the new hood is installed and certified. Mr. Cadden stated the new hood is not in use yet while he is awaiting the approval of the MABP.

NECC is planning on marketing and selling compounded products in all 50 U.S. states per Mr. Cadden. He stated he is in the process of applying to each state in order to do so. Currently he estimated he has permission to do so from approximately 13 states, though he could not recall which specific states. Mr. Cadden stated his firm employs individuals that telephone and/or send correspondence to prospective customers (physicians and medical facilities) found on the internet or in telephone books. He stated this is done to find prospective in-state and out-of-state customers. He also stated that he intends to have a representative from his firm travel the state of Massachusetts to promote the firm's services to potential customers. The firm also maintains a web site which advertises the firm's services and contains downloadable order forms. Mr. Cadden stated the NECC web site does not accept orders on-line.

COORDINATION WITH MASSACHUSETTS STATE BOARD OF PHARMACY

The Massachusetts Board of Pharmacy (MABP) provided three representatives who were each present intermittently throughout the inspection. The representatives were Leslie Doyle, RPh., Supervisory Investigator, James Emery, Investigator, and Arthur J. Chaput,

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Quality Assurance Surveyor. To facilitate the sharing of information with MABP, one of the MedWatch complainants was contacted regarding directly reporting the adverse events to the MABP. MABP representatives were present throughout the majority of the inspection, which further facilitated MABP and FDA communications. In early 2002 the MABP designated a committee to formulate compounding regulations for the State. Currently these regulations are under review by MABP. MABP anticipates implementing these new regulations sometime in 2003. Mr. Cadden is a member of the committee assigned by MABP.

Correspondence to the MABP should be sent to the following address:

The Commonwealth of Massachusetts
Division of Professional Licensure
Office of Investigations
239 Causeway Street, Suite 400
Boston, MA 02114
(617) 727-1803

MEDWATCH COMPLAINTS

This investigation was conducted per the HFM-330 assignment issued to the New England District Office. The assignment requested the collection of information and samples of NECC products in association with MedWatch complaints. Three MedWatch reports were received by the FDA detailing adverse events that occurred in two patients in July 2002 at the (b) (6), (b) (7)(C). See Attachment #1 for the HFM-330 assignment and three MedWatch reports. In the MedWatch reports, the complainant attributed the adverse reactions to a compounded methylprednisolone acetate preservative-free 80mg/ml injectable prepared by NECC in May 2002. The MedWatch complaints were reported by a physician and the Chief Pharmacist at (b) (6). The Chief Pharmacist and Quality Supervisor from (b) (6) were both contacted regarding the MedWatch reports and events surrounding the adverse reactions.

On 9/30/02, Inv. Joyce spoke with the Chief Pharmacist (b) (6), (b) (7)(C). He stated that after the adverse reactions occurred, he instructed his staff to remove all the methylprednisolone acetate injectable with the affected lot number from the hospital floors. The collected vials were then turned over to the hospital's Quality Assurance personnel. The MedWatch report from the pharmacist stated samples were available.

On 9/4/02, 11/1/02 & 3/3/03 Inv. Joyce spoke with (b) (6), (b) (7)(C), Quality Supervisor at (b) (6). On 9/4/02, Inv. Joyce confirmed with (b) (6), (b) (7)(C) that samples were available. (b) (6), (b) (7)(C) stated that she had received the unused vials from the pharmacy department. Arrangements were made with the FDA New York District to collect the sample vials (b) (6), (b) (7)(C).

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(b) (6), (b) (7)(C) was able to describe the adverse events and surrounding incidents. She stated that both patients were given injections on (b) (6), (b) (7)(C) from the same lot (05312002@16) and both experienced pain and headache and were hospitalized with meningitis-like symptoms. Both patients received antibiotic therapy. Cultures of both patients' cerebrospinal fluid (CSF) were negative. Since both patients were on antibiotic therapy, the CSF cultures would be negative regardless of microbial growth prior to treatment. (b) (6), (b) (7)(C) did not have a hard copy of the CSF results. Both patients fully recovered. (b) (6), (b) (7)(C) confirmed the route of administration for both patients was intrathecal. One injection was intended as intrathecal and the other was unintended intrathecal (misplacement of needle into an unintended adjacent space).

One of the MedWatch reports stated the vials tested positive for gram negative organisms. Attached as Exhibit #1 is the fax from (b) (6), (b) (7)(C) reporting results of the vial testing performed by (b) (6). The lab results show initially there was growth (gram negative rods), but after 8 weeks incubation there was no growth seen. (b) (6), (b) (7)(C) stated she believes the vial tested was from lot 05312002@16 and that the lab results are under one of the patient's names, but she believes it was the vial tested, not patient fluids (ie., not cerebrospinal fluid). Since they are single-dose vials, the actual vials used on the affected patients were discarded and could not be located.

When asked about actions taken by (b) (6), (b) (6), (b) (7)(C) stated she first contacted Mr. Cadden at NECC to make him aware of the adverse events. She stated she spoke with Mr. Cadden on/about 7/23/02. She stated she does not believe (b) (6) returned any of the vials to NECC. She believes they were all retained for FDA sampling and hospital investigative purposes. After the adverse events occurred, a hospital committee (including infectious disease and anesthesiology) looked into possible causes and determined, for lack of another answer, that the adverse events were caused by the compounded product from NECC.

SAMPLE COLLECTION BY FDA NYK DISTRICT: SEPTEMBER 9, 2002

A sample (FACTS 193610) was collected on 9/12/2002 by the New York District. The sample consisted of sixteen (16) vials of methylprednisolone acetate preservative-free (80mg/ml) injectable with "same lot number suspected for causing adverse reactions" in MedWatch reports. The sample was sent to FDA NRL for sterility and endotoxin testing. NRL was unable to perform the sample analysis until 4 days after the compounded product's expiration date. See Attachment #2 for the collection report.

NOTE: The NRL reported the vials collected at (b) (6) were from lot 051902@15, a different lot than the MedWatch reports. A NWE-DO Compliance Officer spoke with (b) (6), (b) (7)(C), Quality Supervisor at (b) (6) on 12/12/02. (b) (6), (b) (7)(C) was surprised that the lot sampled by FDA at (b) (6) was different than the lot indicated in the MedWatch reports. This issue was not resolved in their phone conversation. (b) (6)

On 12/11/02, the NRL reported positive results for sterility (gram negative organisms). On 12/12/02 Investigators Joyce and Dewoskin visited the firm to notify Mr. Cadden of

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the positive sterility results found upon analysis of his compounded product (see below for full description of firm visit).

On 12/18/02, NRL reported that the organisms were identified as *Burkholderia cepacia* and *Sphingomonas paucimobilis*. The following is an NRL Pharmaceutical Microbiologist's description of the organisms found in sample 193610:

"Description of each bacterium:

Burkholderia cepacia- Burkholderia are aerobic, non-spore-forming, gram-negative rods which are straight or curved. This type of bacteria are environmental organisms found in water, in soil, and on plants including fruits and vegetables. "Because of their ability to survive in aqueous environments, these organisms have become particularly problematic in the hospital environment". "The genus Burkholderia contains two organisms frequently encountered as human pathogens, *B. pseudomallei* and *B. cepacia*". "B. c. is well recognized as a nosocomial pathogen causing infections associated with contaminated equipment, medications, and disinfectants including povidone-iodine and benzalkonium chloride". "B.c. is emerging as an important pathogen in two patient populations with genetic diseases, Cystic fibrosis, and chronic granulomatous disease"

Sphingomonas paucimobilis- This group of bacteria is also an aerobic non spore forming, gram-negative rod. "The new genus Spingomonas was created for the organism formerly known as Pseudomonas paucimobilis and CDC Ilk-1. The genus Sphingomonas presently contain 16 species, but only *S. paucimobilis*, which is designated the type species, is important clinically. Colonies grown on blood agar medium are yellow pigmented and slowly growing, with only small colonies observed after 24 hr of incubation. S.a. is widely distributed in the environment, including water, and has been isolated from a variety of clinical specimens, including blood, cerebrospinal fluid, peritoneal fluid, urine, wounds, vagina, and cervix and from hospital environment"

The source of the reference information was obtained from the Manual of Clinical Microbiology, 7th edition, 1999, published by the American Society for Microbiology".

Please refer to the following table for a description of NYK district samples collected and the subsequent NRL results.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
193610	Methylpredisolone AC (PF) 80MG/ML INJ	05192002@15	16	11/15/02	1/14= <i>Sphingomonas paucimobilis</i> 4/14= <i>Burkholderia cepacia</i>

VISIT TO FIRM: OCTOBER 24, 2002

MABP Supervisory Investigator Leslie Doyle accompanied Inv. Joyce to the firm. Ms. Doyle presented Mr. Cadden with a formal request for information. At that time she

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informed Mr. Cadden that a copy of his response would be provided to the FDA. Please see Exhibit #2 for the State's request for information and NECC written response.

Mr. Cadden stated he was telephoned by an employee from (b) to notify him of the adverse reactions that were reported to MedWatch. He did not have the employee name, but did email that information to me the following day (Exhibit #3). (b) (6), (b) (7)(C) Quality Supervisor at (b) notified Mr. Cadden about the adverse reactions associated with methylprednisolone (6) acetate. Mr. Cadden stated (b) (6), (b) (7)(C) told him the adverse reactions were due to "administration errors" since the injections were administered intrathecally. The medication is not FDA approved for intrathecal administration. Mr. Cadden stated that the hospital had returned vials of the affected product to the firm and that NECC sent a sample of the returned product to its contract laboratory (Analytical Research Laboratories, Oklahoma City, OK (ARL) for testing. I viewed the laboratory results (received by lab on 8/20/02 and reported on 8/22/02). The results reported on 8/22/02 hard copy were negative for "endotoxin content and microbial contamination". I then viewed the initial ARL results (received by lab on 6/19/02 and reported on 6/20/02) for the affected lot, 05312002@16, which were negative for "endotoxin content and microbial contamination". See Exhibit #4 for supporting documentation.

The following information was also obtained from Mr. Cadden:

- 1) Random sampling for finished compounds is as follows: for lots with small volume vials, 2-3 vials are tested and for lots of larger volume vials (ie., 10ml) 1 vial is tested for sterility and endotoxins.
- 2) NECC is still closed on Saturday and Sunday, but Mr. Cadden stated he often comes to work on Saturdays to make sterile compounds. Mrs. Cadden still works two to three days per week in an administrative role only.
- 3) Regarding the processing of sterile suspension injectable steroids: The compounding occurs in the "Clean Room". Once compounded, the suspension (in a beaker) is covered with 3 layers of aluminum foil, brought through the ante-room to the main compounding area and autoclaved. The suspension is then brought back through the ante-room into the "Clean Room". The suspension is brought to room temperature on a magnetic stirrer (approximately 2-4 hours) then the suspension is transferred to vials (various sizes) with a Baxter Repeater Pump. Mr. Cadden stated the bulk suspension is sterilized (versus sterilization in final vial container) because the properties of the suspension would not allow it to resuspend in the vials and the particle size would be too large. The steroid compounding formulas from Professional Compounding Centers of America, Houston, TX (PCCA) instruct him to compound the products in this way. Suspensions must be autoclaved since they cannot be filtered through a 0.22µ filter due to particle size.

Ms. Doyle told Mr. Cadden that MABP discourages the use of "as directed" instructions on patient prescription labeling and that stock sold as "For Office Use Only" was not allowed in the state of Massachusetts unless the firm obtained a special permit.

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VISIT TO FIRM: DECEMBER 12, 2002

On 12/11/02, NRL informed NWE-DO that the sterility results for sample 193610 showed a presumptive positive for four (4) of fourteen (14) vials. At that time it became a priority to visit NECC to inform Mr. Cadden of the results and determine what his intentions would be regarding the compounded product. On 12/12/02, Inv. Joyce and DeWoskin went to NECC and informed Mr. Cadden of these results. Mr. Emery and Mr. Chaput from the MABP were present. Mr. Cadden stated that NECC had conducted a recall of the product in August 2002 (without FDA knowledge) after the adverse reactions were reported to NECC by the MedWatch complainant hospital. Mr. Cadden did not share this recall information with the FDA at the October 2002 visit to NECC. He stated recall notification to customers was done via telephone calls. The only record of the recall process was a three page table listing customer names, returned product and lot numbers. Recall information was requested per NWE-DO Recall Coordinator guidance.

Mr. Cadden confirmed prior to the recall he was using 6 month expiration dates for sterile products with preservatives and was sterilizing the vials himself at NECC. He stated he conducted a recall after receiving the complaint from (b) in July 2002. He stated he received 500-600 vials back from customers as a result of the recall. He retested one (1) of these vials for sterility and endotoxin and the results were negative. Mr. Cadden showed us ARL #24399 results (refer to Exh. #4, pages 3&4). I asked Mr. Cadden if he thought of testing a more representative quantity from the returned product (i.e., not just one vial), but he stated he only tested one vial. Mr. Cadden stated the corrections he has made since the complaint from (b) include the following actions: 1) expiration date was decreased from 6 months to 60 days for preservative free products, and 2) utilization of a contract facility (Eagle-Picher) to pre-sterilize vials for use in sterile products. See Exhibit #5 for information from Eagle-Picher Industries, Inc. website (Miami, OK).

Mr. Cadden stated he had not received any other complaints associated with the use of NECC compounded sterile steroid injectables. Representative testing for sterility and endotoxin was discussed with Mr. Cadden. We explained to Mr. Cadden that the USP contains guidance on sample sizes in relation to lot quantities. We also discussed validation and verification of testing procedures performed by contract laboratories.

While at the firm, samples were collected of methylprednisolone acetate preservative-free (PF) injectable and betamethasone repository injectable. After seeking supervisory guidance, I collected 20 x 1 ml vials of methylprednisolone acetate PF (80mg/ml) and 10 x 5ml vials of betamethasone repository (6mg/ml betamethasone repository = 3mg betamethasone sodium phosphate + 3mg betamethasone acetate). These compounds were chosen because they were associated with the current and April 2002 MedWatch reports. Both products are sterile suspension injectable steroids and are compounded by similar methods according to Mr. Cadden. See Attachment #3, 4, & 5 for the FDA-463a (Affidavit), FDA-484 (Receipt for Samples), and collection reports.

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Please refer to the following table for a description of samples collected on this date and the subsequent NRL results.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
169126	Methylprednisolone AC (PF) 80 mg/ml x 1 ml	11262002@4	20	1/25/03	Assay= Within Range
169127	Betamethasone Repository (PF) 6mg/ml x 5ml (BSP+BA)	11302002@1	10	1/29/03	Assay= Subpotent BSP 77.4 (O); 74.6 (C/A) BA 71.6 (O); 71.0 (C/A)

VISIT TO FIRM: DECEMBER 18, 2002

A visit to the firm was conducted to request information regarding NECC recall procedures and collect samples. After conferring with NRL for sampling requirements, it was decided that further samples were necessary from NECC. See Attachment # 6, 7 & 8 for the FDA-463a (Affidavit), FDA-484 (Receipt for Samples), and collection reports. Please refer to the following table for a description of samples collected on this date and the subsequent NRL results.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
169128	Methylprednisolone AC (PF) 40 mg/ml x 1 ml	11262002@5	50	1/10/03	Sterility= Negative Endotoxin= "not performed" Assay= Superpotent 131.4 (O) & 133.1% (C/A)
169129	Betamethasone Repository 6mg/ml x 2 ml	12102002@11	50	6/8/03	Sterility= Negative Endotoxin= Negative Assay= subpotent BSP 67.0 (O); 62.0 (C/A) BA 59.8 (O); 58.7 (C/A)
169130	Methylprednisolone AC (PF) 80 mg/ml x 1 ml	11262002@4	50	1/25/03	Sterility= Negative Endotoxin= Negative
169131	Triamcinolone Acetonide 40 mg/ml x 5 ml	11202002@8	34	2/18/03	Sterility= Negative Endotoxin "not performed"
169132	Prochlorperazine Edisylate 5 mg/ml x 10 ml	11112002@11	18	2/9/03	Sterility= Negative Endotoxin "not performed"
169133	Saline PF 10% Injectable x 15 ml	12122002@14	5	3/12/03	Sterility= Negative Endotoxin= "not performed"
208553	Betamethasone Repository (PF) 6mg/ml x 2ml	11302002@1	50	1/29/03	Sterility= Negative Endotoxin= "not performed"

1. PF= Preservative Free (for some products, NECC makes product both with and without preservative)
2. Betamethasone Repository= Betamethasone Sodium Phosphate & Betamethasone Acetate.

The following items were also discussed with Mr. Cadden:

- 1) Sampling of compounded products by NECC: The firm's sampling procedures were again discussed with Mr. Cadden. He stated he used the recommendations of his contract laboratory (ARL). I discussed with Mr. Cadden the USP recommendations for testing of sterile products. Mr. Cadden stated he would look at these recommendations and reconsider his testing procedures. A copy of the firm's sample log to ARL is attached as Exhibit #6.
- 2) Environmental Monitoring of "Clean Room": While discussing the firm's "clean room", Mr. Cadden stated that he has his laminar flow hood serviced yearly,

which includes HEPA filter testing (and replacement as necessary). I asked Mr. Cadden if he would know if the HEPA filter needed to be changed between yearly inspections and he stated no. I discussed with Mr. Cadden the impact that could have by possibly compromising the sterility of his product. I recommended NECC initially evaluate the life span of their HEPA filters (via more frequent monitoring) and compose a testing plan around that evaluation. Mr. Cadden stated that the firm changes the pre-filters every 4-6 weeks to prolong the life of the HEPA filter. Mr. Cadden stated another component of his yearly testing of the clean room is air sampling. I recommended Mr. Cadden consider expanding his environmental monitoring to include surface and wall sampling. I suggested guidance resources such as the USP.

3) Sterile compound preparation:

- a. Mr. Cadden stated that he uses a new set of disposable tubing for the Baxter Repeater Pump for each lot that is compounded.
- b. When asked what other sterile compounds are made by the firm, Mr. Cadden stated if he was able to filter the product that he would make the compound.
- c. Mr. Cadden stated the water source for sterile products comes from 1000 ml bags of Sterile Water for Injection.
- d. Mr. Cadden stated that NECC started to compound Prochlorperazine (Compazine) Injectable 2-3 weeks prior when he was able to access the bulk product.
- e. Mr. Cadden stated the firm does not dispense any medication to clients for office stock use. He stated that it would be a possibility in the future if Massachusetts state laws changed and allowed this of compounding pharmacies.
- f. Inv. Joyce and DeWoskin requested of Mr. Cadden the opportunity to observe production of sterile products in the very near future depending on his compounding schedule. On 12/23/02, Inv. DeWoskin spoke with Mrs. Cadden who stated that compounding would not resume until after the start of the New Year since business was slow around the holidays.
- g. A copy of the NECC "Policies and Procedures for Compounding Sterile Products" and "Aseptic Compounding Policies and Procedures Manual" (SOP's) are attached as Exhibit # 7 & 8.

4) Recall Procedures:

- a. Health risk analysis: While discussing the lots made before August 2002 that were distributed with a 6 month expiration date, I asked Mr. Cadden if he had any intentions of recalling those products also since those products will continue to have expiration dates through February 2003. Mr. Cadden stated he did not have any intention of recalling products other than the steroid products recalled in August 2002. The firm's recall procedures in August 2003 consisted of calling clients who received the 05312002@16 lot of methylprednisolone and asking them to return any steroid product they had in stock. This means that clients who received lots other than the 05312002@16 were not notified of the recall or

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- possible problems with the products and will likely use those products until the expiration date of 6 months.
- b. Mrs. Cadden stated she notified customers of the recall by telephone. We restated the information needed by FDA to process the recall. Please see the heading "Recall Information" for the information provided by NECC.
 - c. The returned products from the recall were still at NECC. Two large boxes were examined by Inv. Joyce. Lot numbers and product names were identifiable and it was confirmed that they were the products intended for the recall.
 - d. A copy of a FDA Talk Paper from 11/15/02 was given to Mr. Cadden and is attached as Attachment #9. This reference described current regulatory actions taken against compounding pharmacies.

VISIT TO FIRM: JANUARY 14, 2003 this section written by Daryl A. DeWoskin)

On 1/14/03, I (Daryl A. DeWoskin) went to NECC. At the time of my arrival I showed my credentials and issued an FDA 482 to Barry Cadden. The purpose of this visit was to pick up a sample of sterilized vial stoppers and sterilized vials. The vial stoppers Mr. Cadden stated are bought pre-sterilized from Eagle Picher Environmental. Mr. Cadden provided CSO DeWoskin with a sealed bag containing 100 vials from Eagle Picher Environmental which was submitted to Northeastern Regional Laboratory (NRL) for sterility and endotoxin testing. These vials are assigned Sample Number 167876. Also on this same date Mr. Cadden provided a sealed bag of vial stoppers which he stated he autoclaved. However, when I returned to the office, I noticed a tear in the bag; and therefore decided not to submit this sample. Instead I decided to go to NECC the following day for a new sample. When the tear was noticed I called the firm and notified Beverly Gilroy, the Educational Coordinator, that I would be returning on 1/15/03 to collect some more autoclaved stoppers.

When I was at the firm on 1/14/03 Barry Cadden notified me that his lawyer (John Tamkin in Newton Massachusetts - phone 617-964-2501) instructed him to tell me that he would provide me samples, but if I had any other requests or questions pertaining to any of their procedures and compounding activities, I was to put my requests or questions in writing. Mr. Cadden stated he would then submit my requests to his lawyer for review, and then get back to me. At the time I was talking to Mr. Cadden I requested the address and name of customers who received lot 05312002@16, methylprednisolone 80mg/ml injection which is a lot number of product that stated he told people to return to NECC due to a potential problem, when I returned to the office I sent Mr. Cadden an e-mail repeating this request. As of 2/10/03, the date that the FDA 483 was issued, a response to this e-mail request had not been received.

VISIT TO FIRM: JANUARY 15, 2003 (this section written by Daryl DeWoskin)

On 1/15/03, I (Daryl A. DeWoskin) returned to NECC for the purpose of collecting a sample of sterilized vial rubber stoppers. I showed my credentials, and issued an FDA

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482 to Beverly Gilroy, Educational Coordinator. Ms. Gilroy said Mr. Cadden was at the facility but not available. At this time she provided me a sample of vial stoppers in a sealed bag which she stated were autoclaved within the last day. I observed that there were water droplets in this bag with the stoppers and that they were making water stains on one part of the white packaging material of the autoclave bag. I submitted these vial stoppers to NRL as Sample #167877. After I was provided the sample by Ms. Gilroy, I left the firm.

Please refer to the following table for a description of samples collected January 14-15, 2002 and the subsequent NRL results.

SAMPLE	PRODUCT	LOT	QTY	Exp	Results
167877	Sterile Vials	n/a	~100	n/a	"In progress" as of 3/4/03
167876	Vial stoppers	n/a	Unkn.	n/a	"In progress" as of 3/4/03

MEETING WITH THE MABP: FEBRUARY 5, 2003 (Boston, MA)

A meeting was held to discuss the appropriate course of action for NECC. Attachment #10 contains the minutes of this meeting.

VISIT TO FIRM: FEBRUARY 10, 2003 (Closeout and issuance of FDA-483)

On 2/5/03, Inv. Joyce telephoned and left a voice mail for Mr. Cadden to inform him that there were violative sample results for subpotency and that the close out meeting would be held on 2/10/03. On 2/6/03, Inv. Joyce received a voice mail from Mr. Cadden stating his intentions to investigate and institute a recall of betamethasone repository (lot 12102002@11).

The purpose of 2/10/03 closeout meeting included issuance of the FDA-483 (List of Observations), to request recall information for the methylprednisolone acetate recalled in 2002, to inform the firm of the complete results for samples obtained 12/18/03, and to find out the firm's intentions with respect to the violative lot within expiry and surrounding lots of similar products.

The closeout meeting took place at NECC on 2/10/03. In attendance from NECC were Barry J. Cadden, NECC Owner and Director of Pharmacy, Doug Farquhar, Esquire, Hymen, Phelps & McNamara, P.C. Ms. Beverly Gilroy, Educational Coordinator, was present in a secretarial role for NECC. In attendance from MABP Leslie Doyle and James Emery. In attendance from the FDA NWE-DO were Investigators Joyce and DeWoskin.

The visit began with a tour of the newly completed room that houses NECC's new Class 10 hood. The hood was certified by Scientific Air Analysis, Inc. (47 Fatina Dr, Ashland, MA 01701, (800) 287-7100). The room contains the Class 10 hood, autoclave, incubator, sink, dishwasher, computer station and office area.

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Mr. Cadden stated NECC had plans to work with a consultant, Eric L. Brennan, of the Preble Group. See Exhibit #9 for the consultant information.

The following information was requested at the meeting:

- 1) For the recall of methylprednisolone acetate in 2002: distribution list (including addresses), reason for recall, recall strategy, time period of product distribution, total quantity distributed, total quantity returned in the recall, documentation of calls to clients, time period in which recall was conducted (start & stop), total quantity made and total put into vials, vial sizes and quantity of each that was made and product disposition.
- 2) For the pending recall of betamethasone repository (lot 12102002@11): all information above applicable to pre-recall period, copy of product labeling, recall initiation date, any complaints or adverse events reported and a recall contact.
- 3) Other Information: consultant CV, list of current stock on hand for all sterile injectable products, list of compounding that has taken place since 1/1/03 for all sterile injectable products and intentions with respect to similar products (ie., sterile injectable steroid suspensions).

Ms. Doyle issued a new request for information from MABP dated 2/7/03. Ms. Doyle provided a copy of the letter (Exhibit #10).

RECALL INFORMATION

On Friday, 12/13/02, the NWE-DO Recall Coordinator stated the district needed information from NECC to document and classify the recall of the methylprednisolone compounded product. I called Mr. Cadden that afternoon and discussed the need for recall information and to collect a larger quantity of vials for our sample (see below). He stated he would gather the information..

On Monday, 12/16/02, I called NECC to verify the receipt of the e-mail request for recall information and to answer any questions pertaining to the request. I left a message after I was told (by Christine) that Mr. Cadden was "in the clean room". Lisa Cadden returned my call and informed me that Mr. Cadden did not receive my email on Friday. I explained that I sent it as a reply to an email from Mr. Cadden and that I would resend the email the following morning. I also verbally stated the list of requested information for the recall so the firm would have adequate notice. This information was not provided to NWE-DO until after 2/10/03. On 2/14/03, NWE-DO Recall Coordinator received two faxes from Mr. Farquhar containing the information for the NECC recall of betamethasone repository injection (6mg/ml, lot 12102002@11). On 2/18/03, NWE-DO Recall Coordinator received a fax from Mr. Farquhar containing the information for the NECC recall of methylprednisolone acetate (preservative-free, all lots compounded before 7/16/02). Please see Exhibit # 11 & 12 for these documents. On 2/21/03, the NWE-DO received additional information from Mr. Farquhar (via fax) informing the

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FDA of NECC recall of further lots of betamethasone repository. This fax is attached as Exhibit #13.

CDEB ASSIGNMENT & CPG 460.200 (PHARMACY COMPOUNDING)

The responses to the HPM-330 questions were obtained by inspectional visits and information provided by the MA State Board of Pharmacy (when followed by a *).

- 1) *Please determine from the Massachusetts Board of Pharmacy, whether NECC is operating in conformance with the applicable state law regulating the practice of pharmacy? Subsequent to the April 2002 joint FDA-State investigation, and referral to the Massachusetts Board of Pharmacy, what follow-up was done or what sanctions were taken by the Board?*

There were no sanctions taken by the MABP against NECC following the April 2002 investigation. The Board is in the process of approving and adopting new regulations for pharmacy compounding firms. The MA applicable state laws reference the USP. Please see FDA-483 items for deficiencies observed at the firm.

- 2) *Does the NECC continue to fill patient specific prescriptions for each compounded product dispensed?*

NECC dispenses and prepares products in bulk for administration to individualized patients pursuant to a receipt of a valid prescription from a prescriber. Bulk products produced in limited quantities at NECC are not compounded for third parties for resale. (*)

Regarding patient specific information for filling non-sterile prescriptions: Mr. Cadden stated that NECC calls patients to ask them about their current medications for their computer patient profiles. He stated another reason to call the patient before making the compound is to verify the patient wants the compound since they are not usually covered under prescription insurance plans.

- 3) *What types and strengths of sterile products does the pharmacy compound? What quantities are being compounded? Is the pharmacy compounding copies of commercially available FDA-approved products (i.e., products that have the same active ingredient, dosage form, and strength)? (typical batch size follows where known).*

- Hyaluronidase 150u/ml- Discontinued by manufacturer (5,000 ml)
- Triamcinolone Diacetate 40mg/ml- When unavailable (500 ml)
- Methylprednisolone Acetate PF 40mg/ml and 80mg/ml-
Special order when unavailable (1,000 ml)

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- Betamethasone Repository 6mg/ml and PF 6mg/ml- Special order when unavailable. (1,000 ml)

Refer to Exh.#17 & 18 for other products compounded by NECC.

- 4) Does NECC continue to assign unsubstantiated beyond-use dates? (designate expiration dates without basis)

Mr. Cadden stated that beyond use dates are included on each formulation obtained from PCCA. Drug substances received, stored, or used at NECC are obtained only from FDA registered facilities. He stated he uses 6 month expiration dates for sterile products with preservative and 60 days for preservative-free.

It should be noted that samples obtained on 2/18/02 show that sample #169128 of methylprednisolone acetate preservative free (40 mg/ml x 1 ml, lot 11262002@5) had an expiration date of 1/10/03, which is approximately 45 days, not 60 days as stated by Mr. Cadden.

- 5) Please obtain formulation information that will enable us to compare the compounded product formulations with the FDA-approved formulations. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a product that is only slightly different than a FDA-approved product that is commercially available (such as to remove a preservative or coloring agent for an individual patient with an allergy problem). In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the formulation for the particular patient. Does the pharmacy have documentation from the prescribers that demonstrates the medical need for the particular variation of the formulation for each individual patient?

Please see Exhibit#14 for "Logged Formula Worksheets" utilized by NECC

- 6) Does NECC compound drug products (including sterile products) in anticipation of receiving prescriptions? If so, what quantities are compounded on that basis? How do the amounts compare to the amount compounded after receiving valid prescriptions?

Mr. Cadden stated sterile products are compounded before prescriptions are received. In general, approximately a 30 day supply would be maintained by NECC. The exception to this would be sterile products that can be filtered, such as ophthalmic products, which are compounded after receipt of a prescription. We did not have the opportunity to verify quantities compounded versus quantities dispensed on a monthly basis.

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Mr. Cadden stated *non-sterile products* (creams, ointments, capsules, etc) are compounded *after* prescriptions are received.

- 7) Does NECC use commercial scale manufacturing or testing equipment to compound drug products? What are the specific batch sizes that are prepared for each type of sterile product and how often is each batch prepared?

In January 2003, NECC completed installation and certification of a "Class 10" Isolator biological hood. Mr. Cadden plans to begin utilizing this new area once he receives MABP approval. Refer to question 2 for typical batch sizes.

- 8) Does NECC compound any products that have been removed or withdrawn from the market for safety reasons? If so, please obtain documentation.

Mr. Cadden denies the firm compounds any products that have been removed or withdrawn from the market for safety reasons

- 9) Has NECC instituted a formal written complaint system since the April 2002 FDA-State inspection?

NECC does not have a formal written complaint system to date per Mr. Cadden. He stated complaints are still filed under specific facility or patient.

- 10) Has NECC performed any corrective actions in response to the FDA 483 List of Observations issued at the conclusion of the April 2002 inspection?

Mr. Cadden told us the only changes made were in response to the (b) (6), (b) (7) adverse reactions and entailed the following: 1) expiration date was decreased from 6 months to 60 days for preservative free products, and 2) utilization of a contract facility (Eagle-Picher) to pre-sterilize vials for use in sterile products. See Exhibit #5 for information from Eagle-Picher Industries, Inc. website (Miami, OK).

- 11) Annually, how many prescriptions for compounded products does the NECC dispense?

Mr. Cadden estimated NECC dispenses 20,000 prescriptions per year.

- 12) Does NECC ship compounded products out of state? Was any of the lot of methylprednisolone acetate PF80mg/ml referenced in the MedWatch report shipped out of state?

According to Mr. Cadden, NECC does ship compounded products out of state. The lot of methylprednisolone acetate PF referenced in the MedWatch was shipped out of state. On 2/5/03, Ms. Doyle from MABP provided the states

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NECC is licensed in as SC, FL, VA, ME, RI, NH, ID, NE, KS, VT, OH, MO, MT and CT (pending).

13. Does the NECC indicate a website concerning the product they compound?

Yes, the firm advertises services on the intranet at neccrx.com. The contents of the website, www.neccrx.com as of 10/11/02 are attached in Exhibit #15. Mr. Cadden states they do not accept online orders.

14) Please document the processes used to make the Methylprednisolone Acetate Preservative Free 80mg/ml product, including production scale, and any in-process controls.

See "Logged Formula Worksheet" provided by Mr. Cadden (Exhibit #16). This is the formula NECC obtained from PCCA to compound Methylprednisolone Acetate. Production scale varies according to what Mr. Cadden anticipates as need for the compounded product. There are no in-process controls per Mr. Cadden.

15) What quantity of compounded sterile products, including methylprednisolone acetate PF 80mg/ml are on hand for sampling?

We obtained samples of sterile injectable compounds on 12/12 & 18/02. Refer to Exhibit #17 for a list of current inventory as of 2/11/03.

OBJECTIONABLE CONDITIONS

Observation #1

For the preparation of sterile drug products distributed by your firm (such as those intended for injection), there is no adequate documentation available to verify they meet set standards (such as specifications and/or USP limits if applicable) or the shelf life (expiration dating period) of these products. This includes the absence of documentation to verify the following:

- A. Personnel performing preparation steps are not contaminating the finished products.
- B. Workspaces are cleaned and sanitized to prevent product contamination.
- C. Equipment and supplies entering the product preparation area are decontaminated/cleaned to prevent product contamination.
- D. The environment in the area where the filling and closing operations are performed is adequate to prevent product contamination (this includes the lack of documentation pertaining to environmental monitoring in the

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- E. immediate area while product is exposed to the environment, such as during filling and prior to container closure).
- F. All autoclave sterilization processes are suitable for the sterilization of drug product preparation equipment and components (which includes vial stoppers and bulk product). Some examples are:
 - a. Lack of documentation to verify that all critical processing parameters being used are appropriate in ensuring that final products meet all standards (such as sterility). Critical processing parameters include sterilization time, temperature, size and nature of load, and chamber loading configuration.
 - b. Records do not state the actual critical parameters used during processing.
 - c. Lack of documentation to verify that the autoclave itself is maintained and calibrated to perform its intended function.
 - d. The autoclave process used on bulk drug products does not have an effect on stability or product specifications.
- F. The transfer of bulk drug product and equipment from the autoclave (after it went through an autoclave process) from one room to another room in which further preparation steps are performed in a laminar air flow workbench, is not introducing contamination into the finished product. All components, including drug substances, vials, and rubber stoppers, meet set standards making them suitable for their intended use.
- G. Components and process water are not contaminating finished products.
- H. Equipment used to measure the amount of ingredients/components are calibrated and maintained to perform their intended function.
- I. Testing procedures and sampling procedures being performed for all drug products are representative of the lots/batches being tested.
- J. That for each preparation of a sterile product or batch of sterile products there has been appropriate laboratory determination of conformity with purity, accuracy, sterility, and non-pyrogenicity, in accordance with established written specifications and policies.
- K. Preparation steps are being performed in a correct manner since batch record preparation instructions are lacking significant preparation steps, which includes mixing procedures.
- L. Final containers are capable of maintaining product integrity (i.e. identity, strength, quality, and purity) throughout the shelf life of the product.
- M. All drug products prepared and packaged at your site meet specifications and USP limits (if applicable) for the expiration dating period assigned. According to documentation and your statements, all drug products are assigned an expiration date of 60 days if they do not contain a preservative, three months if they are not filtered, and 6 months if they are filtered. No data was available for any of your products prepared at your firm to support these expiration date periods.

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In addition, for all of the items above there were no written procedures available pertaining to the performance of these duties and processes.

Discussion of FDA 483 Observation 1

Mr. Cadden stated he did not have documentation of established standards or specifications for finished sterile products compounded by NECC. This included the verification that the above items (A thru M) have been addressed by NECC to ensure the quality of products compounded by NECC.

Mr. Cadden stated he was unable to provide data to support the assigned shelf life for finished sterile products compounded by NECC. Mr. Cadden stated that he utilized the recommendations on the product compounding formulas ("logged formula worksheets") received from PCCA. After learning of the the adverse reactions to methylprednisolone acetate in July 2002, Mr. Cadden stated he shortened the shelf life of preservative-free products from 6 months to 60 days. There was no product specific data available to support the use of either shelf life.

Mr. Cadden stated that he purchased Standard Operating Procedure (SOP's) from PCCA. After review of the SOP's, it was determined that they have not been revised for use at NECC. It was also noted that NECC does not follow the SOP's. Mr. Cadden stated he does not follow all of the SOP's. Refer to Exhibit #8 for the NECC SOP's.

Observation #2

There are no written procedures pertaining to the handling of complaints, nor does your firm maintain a complaint file.

Discussion of FDA 483 Observation 2

Mr. Cadden stated that no formal complaint files are maintained by NECC. NECC has not established adequate written procedures for the handling of complaints and adverse events reported to the firm.

Observation #3

There was no documentation available for the handling and disposition of reports of patient problems, complaints, adverse drug reactions, drug product or device defects, and other adverse events reported. For example, after a medical facility reported adverse events associated with lot 05312002@16, your firm conducted a

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recall of injectable steroid products and implemented shorter expiration dates and use of pre-sterilized vials. You stated you have no documentation available pertaining to an investigation being performed for this and other related lots which shows that adequate follow-up action was taken.

Discussion of FDA 483 Observation 3

Mr. Cadden stated he did not have documentation of an investigation or the subsequent changes made by NECC in response to the adverse events associated with methylprednisolone acetate lot 05312002@16. No written records were available to rationalize or confirm the implementation of shorter expiration dates and the use of pre-sterilized vials. There was also no written documentation to show follow up actions were being taken to ensure the effectiveness of corrective actions taken by the firm.

DISCUSSION WITH MANAGEMENT (2/10/03)

It was explained to Mr. Cadden that at this point the FDA is considering NECC a pharmacy compounder and not a drug manufacturer. Mr. Cadden stated he had retained the services of a pharmaceutical consultant. The consultant is supposed to meet with Mr. Cadden within the next week to determine a course of action.

Inv. Joyce and DeWoskin presented the FDA-483 to Mr. Cadden. Each item was reviewed with Mr. Cadden. Mr. Cadden was asked if he understood each point, to which he answered yes. Mr. Cadden was asked if he had any questions about each of the observation items, to which he answered no. Mr. Farquhar stated he was very familiar with the observations and would be able to assist Mr. Cadden in his written response.

Further details pertaining to this closing discussion is in this report under the heading entitled: "Visit to Firm: February 10, 2003". Mr. Farquhar stated they planned to have a written response to the FDA within two weeks. After the FDA-483 was issued and discussed, the inspection was concluded.

REFUSALS

Though information was not made readily available, there were no direct refusals from the firm.

ADDITIONAL INFORMATION

Guidance was received from HFM-330 throughout the entire investigation, including a teleconference on 12/16/02. During this teleconference, guidance was given regarding

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samples to be collected and the composition and issuance of the FDA-483 (List of Observations).

On 1/25/03, NWE-DO received information that NECC had retained the services of Douglas Farquhar, Esq., Hymen, Phelps & McNamara (Washington, DC) to represent him in regulatory matters. Mr. Farquhar requested available information through FOI. Mr. Farquhar discussed with the NWE-DO Compliance Branch that he would be representing NECC and Mr. Cadden; communication between the FDA and NECC from that point on (excluding the closeout on 2/10/03) occurred between Mr. Farquhar and NWE-DO Compliance Branch.

On 3/3/03 Ms. Doyle of MABP related to Inv. Joyce that NECC had retained separate counsel to handle MABP related matters; however, he still retained Mr. Farquhar to handle FDA related matters.

At the time of this report, Ms. Doyle stated MABP had not received a reply from NECC for their request for information dated 2/7/03. NECC requested and was granted an extension for submitting this information to MABP.

The list of current stock on hand for all sterile injectable products was received by fax on 2/11/03 (Exhibit #17). The list of compounding that has taken place since 1/1/03 for all sterile injectable products was received by email on 2/14/03 (Exhibit #18). Mr. Farquhar's response to Ms. Doyle's questions on 2/10/03 regarding FDA regulations was received by NWE-DO on 2/21/03 and is attached as Exhibit #19.

The documents obtained from NECC to support the sample collections on 12/12 & 13/02 are attached as Exhibit #20.

Since the opportunity to observe production did not occur, no photographs were taken by the investigators.

ATTACHMENTS

FDA-482 Notice of Inspection (Dated 10/24/02)
FDA-482 Notice of Inspection (Dated 12/12/02)
FDA-482 Notice of Inspection (Dated 1/14/03)
FDA-482 Notice of Inspection (Dated 1/15/03)
FDA-482 Notice of Inspection (Dated 2/10/03)

- 1) CDER HFM-330 Assignment (Dated 8/2/02, 10 pages)
- 2) Collection Report for NYK Sample 193610 (4 pages)
- 3) FDA 463a Affidavit (Dated 12/12/02, 1 page)
- 4) FDA-484 Receipt for Samples (Dated 12/12/02, 2 pages)

New England Compounding Center
697 Waverly Street
Framingham, MA 01702

FACTS #332851
KMJ/DAD

FBI# 3003623877
EI Start: 10/24/02
EI End: 2/10/03

- 5) Collection Reports for NWE Samples 12/12/02 (6 pages)
- 6) FDA 463a Affidavit (Dated 12/18/02, 1 pages)
- 7) FDA-484 Receipt for Samples (Dated 12/18/02, 2 pages)
- 8) Collection Reports for NWE Samples 12/18/02, 21 pages;
- 9) FDA Talk Paper (Dated 11/15/02, 2 pages)
- 10) Minutes of Meeting between MA State Board of Pharmacy and FDA NWE-DO (with attachments) (Dated 2/24/03, __pages)
- 11) FDA-483 Inspectional Observations (Dated 2/10/03, 3 pages)

EXHIBITS

- 1) Fax from (b) (6), (b) (7)(C) of (b) (6), (b) (7)(C) (Dated 11/1/02, 2 pages)
- 2) MABP Request for Information (10/02) and NECC response (Dated 11/18/02, 10 pages)
- 3) Email from NECC (dated 10/25/01, 1 page)
- 4) Analytical Research Laboratories Results for methylprednisolone lot 05312002@16 (4 pages)
- 5) Eagle-Picher Industries, Inc. background information (6 pages)
- 6) NECC sampling log to ARL (1 page)
- 7) NECC "Policies & Procedures for Compounding Sterile Products" (3 pages)
- 8) NECC SOP Manual (179 pages)
- 9) Curriculum Vitae of NECC Consultant (Fax Dated 2/11/03, 5 pages)
- 10) MA State Board of Pharmacy Request to NECC (Dated 2/7/03, 3 pages)
- 11) NECC Recall information (dated 2/14/03, 9 pages)
- 12) NECC Recall information (dated 2/18/03, 7 pages)
- 13) NECC Recall Information to NWE-DO Recall Coordinator (Dated 2/21/03, 7 pages)
- 14) Logged Formula Worksheets (21 pages)
- 15) NECC website information (Date accessed 10/11/02, 7 pages)
- 16) Methylprednisolone acetate "logged formula worksheet" (1 page)
- 17) NECC current inventory (dated 2/11/03, 2 pages)
- 18) NECC lots compounded since 1/1/03 (dated 2/14/03, 2 pages)
- 19) NECC Response to 503A statement by Ms. Doyle (Dated 2/21/03, 2 pages)
- 20) Supporting documents for sample collections (24 pages)

New England Compounding Center

697 Waverly Street

Framingham, MA 01702

FACTS #332851

KMJ/DAD

FBI# 3003623877

EI Start: 10/24/02

EI End: 2/10/03

Kristina M Joyce

Kristina Joyce, CSO

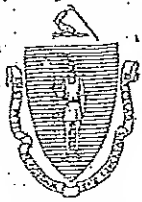
NWE-DO

Daryl DeWoskin

Daryl DeWoskin, CSO

NWE-DO

March 4, 2004, Mass. Bd. Investigation Report
(Mass Bd. Dockets: DS 03 055; and PH 03 066)



MDPH-Division of Health Professions Licensure
INVESTIGATION REPORT

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4A

Licensee Name:

Docket No.

New England Compounding Center
And
Barry Cadden

DS 03 055

PH 03 066

Priority Code: 2 Received by DHPL: 2/12/2003

Docket Opened: 2/12/03
Assigned: 2/12/03

Investigator Name: Leslie S. Doyle, Compliance Officer

Supervisor Name: Jean Pontikas - Director

SECTION I: Demographics and History

A. Licensee Information

1. Name of Licensee/Respondent:

Barry Cadden

2. Address of Record:

[REDACTED]

3. Phone Number(s):

Home: [REDACTED] Cell: (N/A)

Business: (508) 820 0606

4. Licensee/Respondent Date of Birth:

[REDACTED]

5. License Type & No.: PH 21239 Current Status: C Exp. Date: 12/31/04

6. Prior Discipline (explain):

Both pharmacist and pharmacy have prior complaint history - the specifics are stated below.

7. Original Date of Issuance:

DS - New England Compounding Center issued 7/16/1998
PH - Barry Cadden - Manager of record issued 10/9/1990

DS 2848
PH 21239

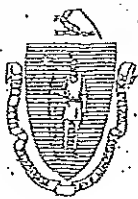
8. Record of Standing attached: ☒ Yes

☐ No

If not, complete item 9 below:

9. Name of Educational Institution Attended:

University of Rhode Island
Date of Graduation: 1990



MDPH-Division of Health Professions Licensure
INVESTIGATION REPORT

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Licensee Name:

Docket No.

New England Compounding Center
And
Barry Cadden

DS 03 055

PH 03 066

Priority Code: 2

Received by DHPL: 2/12/2003

Docket Opened: 2/12/03

Assigned: 2/12/03

Investigator Name: Leslie S. Doyle, Compliance Officer

Supervisor Name: Jean Pontikas, Director

SECTION I: Demographics and History

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Home: [REDACTED] Cell: (N/A)

Business: (508) 820 0606

4. Licensee/Respondent Date of Birth:

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DS 2848

PH - Barry Cadden - Manager of record Issued 10/9/1990

PH 21239

8. Record of Standing attached:

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☐ No

If not, complete item 9 below:

9. Name of Educational Institution Attended:

University of Rhode Island

Date of Graduation: 1990

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INVESTIGATION REPORT
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Licensee Name:

Docket No.

New England Compounding Center
And
Barry Cadden

DS 03 055

PH 03 066

B. OTHER MASSACHUSETTS LICENSES HELD:

1. Profession/Trade: NA

2. License No. Current Status: Exp. Date:

3. Prior Discipline (explain):

4. Certified Documentation Attached ☐ Yes ☒ No

C. NON-MASSACHUSETTS LICENSES HELD:

1. Profession / Trade: Pharmacy licenses are held in all but four states throughout the United States.

2. License No. Current Status: Exp. Date:

3. Prior Discipline (explain):

4. Certified Documentation Attached ☐ Yes ☒ No

D. LICENSEE'S EMPLOYMENT INFORMATION:

1. Current Employer: New England Compounding Center

2. Address: 697 Waverly St. Framingham, Ma 01702

3. Telephone Number: (508) 820 0606

E. COMPLAINT HISTORY:

Companion Complaints: (list docket numbers, allegations, status, and disposition)

Drug Store Prior History and outcome:

20021211ds036 - Board complaint - allegations: unprofessional conduct (JCE) pending board decision - 2/28/03

20032026ds060 - Consumer complaint - (Marsh) allegations: failure to adhere to standards of practice (JCE) - pending board decision 4/1/03

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INVESTIGATION REPORT

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Licensee Name:

Docket No.

New England Compounding Center
And
Barry Cadden

DS 03 055

PH 03 066

Pharmacist Cadden prior history and outcome:

19990330ph066 - Board complaint; allegations: violation of CMR 247 section 9.01(3) (JDC). Informal Reprimand issued for supplying prescriptions blanks to practitioners, dismissed 12/10/99

20021211ph042 - Board complaint - allegations: unprofessional conduct, (JCE) - pending board decision, 2/28/03

20030226ph070 - Consumer complaint - (Marsh) allegations: failure to adhere to standards of practice - (JCE) pending board decision, 4/11/03

- Pending/Related Complaints: (list docket numbers, allegations, status, and disposition)

See above as stated

Criminal Offender Records Information Check (CORI) been performed? ☐ Yes ☒ No
Include certified copies of judgments

SECTION II: Interviews, Complainant Info & Index of Materials/Documents

A. INTERVIEWS CONDUCTED: List below and include labeled interview notes in case file

Individuals Interviewed (name/title)	When/Where? (dates/time of day)	Type Interview (in-person/phone)	Contact Information (phone, address, business)
1.			
2.			
3.			
4.			
5.			

B. WITNESSES NOT AVAILABLE FOR INTERVIEW: Document attempts in case file

Individuals	Contact Information (phone, address, business)	Attempt(s) to contact (dates, times)
1.		
2.		
3.		

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Licensee Name:

Docket No.

New England Compounding Center
And
Barry Cadden

DS 03 055

PH 03 066

C. COMPLAINANT INFORMATION:

A. NAME OF COMPLAINANT: Mass. Board of Registration in Pharmacy
B. ADDRESS: 239 Causeway St. Suite 500 - Boston, MA 02114
C. PHONE NO: (617) 727 9953 CELL PHONE: (n/a)

D. INDEX OF MATERIALS/DOCUMENTS: Label documents/materials as noted below in order of presentation in the file

ITEM A: Complaint	ITEM B: Record of standing
ITEM C: Complaint history	ITEM D: List of Concerns / DHHS/FDA
ITEM E: NECC response to allegations	ITEM F: Air Analysis
ITEM G: NECC P&P Procedures	ITEM H: NECC response to FDA
ITEM I: FDA Letter to Board	ITEM J: Copy of 2/20/2004 Compliance Inspection.

SECTION III: Investigation Summary

A. Allegation of Complaint: give nature code and summarize the allegations:

Complaints as referenced in docket numbers DS 03-055 and PH 03 066 were filed by the Mass. Board of Registration against New England Compounding Center, and Barry Cadden, Manager of record for the facility, based on the failure to adhere to standards of practice for compounding prescriptions. Specifically, the pharmacy and pharmacist engaged in unprofessional conduct as exhibited by; failing to follow guidelines, sterility procedures, record keeping requirements, batch records, failing to provide certificates of analysis, proof of sterility testing, Endotoxin test results, batch numbers and prescriptions upon request.

B. Setting Where Alleged Incident/Conduct Occurred:

1. Facility or Business Type: Pharmacy - Compounding Pharmacy
Name: New England Compounding Center
Address: 697 Waverly St. Framingham, Ma 01702
Phone No: 508 820 0606
Contact Person: Barry Cadden
Contact's Title: Manager of Record

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INVESTIGATION REPORT

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Licensee Name:

Docket No.

New England Compounding Center
And
Barry Cadden

DS 03 055

PH 03 066

2. Licensee's Supervisor (if applicable give name): not applicable
Phone No: N/A

C. Attorney of Record

1. Name of Attorney:

Attorney John Tamkin	617 964 2501
Attorney Jeff Gibbs	202 737 4288
Attorney Paul Cirel	617 371 1025
Hyman, Phelps, McNamara	202 737 5600

For FDA concerns:

Attorney Douglas B Farquhar 202 737 5600

2. Name of Firm:

3. Address:

4. Phone Nos.

D. Answer of Respondent (summarize licensee's response to allegations):

Licensee denied the allegations and has submitted copies of policy and procedures along with corrective measures.

E. Investigator's Activities and Findings:

Describe in narrative format - who, what, where, when, and why and include citations to laws and regulations when applicable to the case.

The Mass. Board of Registration in Pharmacy has filed a complaint against New England Compounding Center (NECC) and Barry Cadden, Manager of record, as it relates to the standards and procedures, sterility, record keeping, certificates of analysis, sterility testing, Endotoxin test results, compound formulations, and batch records for product compounded as such records could not be produced and matched up to dispensed prescriptions.

Based on a confidential report submitted on a Med. Watch form to the District Office of the Food and Drug Administration (FDA) in Stoneham, it is alleged that NECC compounded Betamethasone Repository Injection 6mg/ml. pursuant to patient specific prescriptions, and delivery to an unnamed medical facility where the medication was administered to patient(s). It is alleged that the patient(s) had an adverse event after the administration of this compounded drug. In both instances the drug was prepared by New England Compounding Center.

During the compounding and preparation process at NECC lot numbers were assigned to the product. Mr. Cadden could not produce an accountability of the product compounded. The FDA was concerned regarding a specific date the Batch of Betamethasone Repository 6mg/ml was compounded. The error was first reported in March 2002. The unnamed facility conducted sterility and Endotoxin tests on the product prepared by NECC, the results indicated a positive test for Endotoxin.

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INVESTIGATION REPORT

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Licensee Name:

Docket No.

New England Compounding Center

DS 03 055

And

Barry Cadden

PH 03 066

Mr. Cadden explained that at the time of preparation, lot numbers were assigned to each patient, however, upon request to review such documentation Mr. Cadden could not provide records for the lot number identified by FDA. Mr. Cadden stated while the lot number was generated, the medication was not dispensed. However, there was no notation to indicate such and, further no prescriptive records could be provided, nor could any certificates of analysis, Endotoxin test results, sterility test results, procedures on aseptic techniques or records indicating training of staff was provided.

When asked to describe his compounding process for the Betamethasone Repository Injection 6mg./ml. Mr. Cadden stated he used Sodium Carboxymethylcellulose, as a suspending agent. After the suspending agent was added the product was placed in the IV hood located in the IV room to cool for up to 4 hours. A sample is taken and sent to the test lab (Analytic Research Lab 840 Research Parkway, #546 Oklahoma City Oklahoma 73104.) Testing may take up to seven days, and during this time the product remained in the hood capped with foil.

Mr. Cadden also stated the medication was being administered via the epidural route, a non-approved route of administration. In response to this incident, NECC changed the suspending agent to Polyglycol.

CORRECTIVE MEASURES:

In February, 2003, Mr. Cadden responded to the allegations with corrective measures in February 2003 stating that he hired a consultant to develop policy and procedures. (Mr. Eric Brennan). All technicians are now certified and registered with the Board of Pharmacy. All staff receives training from Pharmacy Compounding Center of America (PCCA) in Texas after six months of employment. In addition:

- 1) All chemicals purchased are in date; beyond use dates are included on each formulation. All products are ordered from FDA registered facilities.
- 2) PCCA provides formulations for compounding.
- 3) Certificate of analysis for all chemicals are now kept on site.
- 4) Analytical test results are obtained and kept on site.
- 5) Log sheets are current and up to date reflecting product name, active ingredients, expiration dates, manufacturer lot numbers, pharmacy lot numbers, name of patient, and Rx number. Expected yield will be included on all log sheets for each compounded product. All prescriptions can be traced back to a lot number thus enabling the pharmacist to trace product in the event of an adverse event or recall.
- 6) Policy and procedures are on site, and employees read and sign a statement of understanding.
- 7) Random samples are routinely collected and sent to an independent lab for sterility, and Endotoxin (pyrogenicity) testing. Remainder lots are placed in a quarantine area i.e.: refrigerator if needed, pending test results. Products of same lot are not re-tested in future. Samples are collected and microbial tests are completed to ensure the products are sterile. Each bulk lot of sterile end products must be tested for sterile Endotoxin, and fungal growth by an independent lab.
- 8) NECC has implemented an aseptic process validation protocol similar to USP 25-NF21 < 1211 (NECC-SOP 7.20).
- 9) When product becomes outdated, it is placed in a designated area until it can be destroyed.
- 10) NECC has obtained the services of a DEA reverse distributor.

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INVESTIGATION REPORT

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Licensee Name:

Docket No.

- 11) NECC dispenses and prepares products for compounding pursuant to a valid patient prescription obtained from a prescriber, and reduced to writing on an approved prescription blank.
- 12) In January 2003 NECC changed to a Class 10 Microenvironment for preparation of all sterile products. / Injectables. Autoclaves are used to sterilize products and vials.
- 13) NECC did conduct the recall requested by the FDA both in writing and by means of telephone communication on 2/14/03.
- 14) Sterilized vials are purchased from an outside vendor. Rubber stoppers are rinsed in sterile water to remove particulate matter and then autoclaved according to SOP.
- 15) SOP for weighing balances has been developed and printouts are attached to log sheets.
- 16) Formulation logs include examination of end product for closure, integrity, color, clarity, and presence of visible foreign particles.
- 17) Documentation of calibrations of a Baxa Repeater Pump and maintenance of all measuring equipment is now located in SOP and are in effect.
- 18) SOP's are in place for sterile and non-sterile compounded product.
- 19) SOP's are in place for complaints and for tracking of complaints.
- 20) All USP and NF guidelines are followed.
- 21) NECC uses NABP's Model Rules, adheres to CMR 247, FDA 795 (non-sterile products), 1206/797 (sterile products) and Chapter 460.200.

Describe documentation/facts that support allegations:

In April, 2002, the Board had the following concerns:

- 1) Pharmacy continues to reduce to writing orders on bulk purchase order forms and not on approved prescription blanks. An issue previously addressed with Mr. Cadden.
- 2) Batch logs are not initialed or signed by technicians preparing the compound.
- 3) Expiration dates are not current on the batch logs. (Mr. Cadden stated that the expirations dates upon receipt of the product were entered into the computer however, they were not updated upon filling of the prescriptions.)
- 4) On some occasions wholesalers would not furnish certificate of analysis.
- 5) Calculations performed by technicians were not documented on the prescription and no pharmacist verification documentation to ensure the calculations were accurate.
- 6) Prescriptions are not filed in a timely manner.
- 7) Perpetual inventory for control substances schedule II performed every 30 days.
- 8) Copies of DEA Licenses are not kept at the pharmacy, but at the licensee's home.
- 9) Copies of CMR 247 not on location, biennial inventory not available for review, technicians were not wearing name badges.
- 10) Pharmacy did not have a reverse distributor for recalled and / or out of date product.
- 11) Pharmacy had no written documentation that technicians review technician rules and regulations as they relate to CMR 247, or, any facility policy and procedure as they relate to compounding, or registration exams.

In October, 2002, Board had the following concerns: FDA investigators informed the Mass. Board of Pharmacy that a second incident involving NECC occurred. The compounded product was identified as Methylprednisolone Acetate.

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INVESTIGATION REPORT

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Licensee Name:

Docket No.

New England Compounding Center
And

DS 03 055

Barry Cadden

PH 03 066

In February, 2003, the Board had the following concerns:

- 1) Batch logs are not initialed or signed by technicians preparing the compound.
- 2) Expiration dates are not current on the batch logs. (Mr. Cadden stated that the expiration dates upon receipt of the product were entered into the computer however, they were not updated when filling of the prescriptions.)
- 3) On some occasions wholesalers would not furnish certificate of analysis, sterility testing, Endotoxin test results, and batch numbers, and corresponding prescriptions could not be provided.
- 4) Prescriptions are not filed in a timely manner.
- 5) Perpetual inventory for control substances schedule II is performed every 30 days.

Describe any information learned or submitted that does not support the allegations:

Food and Drug Administration Investigators agreed that New England Compounding was not manufacturing any product.

Describe any information requested and not received:

All documentation requested from Mr. Cadden as part of this investigation has been provided.

Describe any exhibits not in case file (radiographs, tapes, etc.). Describe location and with whom.
N/A

List other state/federal or municipal agencies involved or also investigating this case and include contact information (name, address, telephone no.)

Food and Drug Administration - Stoneham, MA [redacted]; [redacted] - investigator, [redacted] compliance officer, [redacted] compliance officer, pharmacist.

F. In your opinion should case go to Medical Error Triage?

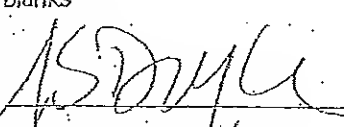
☐ Yes ☒ No

Explain:

G. Summary of alleged violations of regulation/statutes:

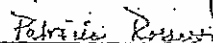
CMR 247.9.01 (3) - prescription pads
CMR 247.9.01 (14) - perpetual inventory
CMR 105.721.032 - prescription blanks
USP and ASHP guidelines

INVESTIGATOR SIGNATURE



DATE MAR 4 2004

SUPERVISOR SIGNATURE



DATE 3/4/04

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INVESTIGATION REPORT

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Licensee Name:

Docket No.

New England Compounding Center
And

DS 03 055

Barry Cadden

PH 03 066

STAFF RECOMMENDATION: Pre-Board Staff Review Date:

Dismissal
Dismissal without prejudice
Dismissal with prejudice
No Violation
Lack of Sufficient Evidence
Advisory Letter

XX Formal Reprimand
Censure
Summary Suspension
Suspension term:

Probation term:

Stayed Probation term:

Continuing Education

Revocation term:

Offer Voluntary Surrender

Non-disciplinary Agreement

Notes:

Based on this pharmacy's history as it relates to prior concerns of the Board agents since 1999, it is this investigator's opinion that a formal reprimand should be issued. At this time February 20, 2004 a re-inspection of the pharmacy indicated that the corrective measures are in place and have been followed through as stated in Mr. Cadden's response to the Board.

BOARD'S Decision/Recommendation: Board Meeting Date:

Dismissal
Dismissal without prejudice
Dismissal with prejudice
No Violation
Lack of Sufficient Evidence

Formal Reprimand
Censure
Summary Suspension
Suspension term:

Advisory Letter

Probation term:

Continuing Education

Stayed Probation term:

Offer Voluntary Surrender

Revocation term:

Notes:

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INVESTIGATION REPORT

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Licensee Name:

Docket No.

Votes:

DISPOSITION OF CASE:

Refer to Board Counsel Date:

Refer to Prosecution Date: 11/1/2011

Other

*September 21, 2004 – Mass. Bd. Meeting Minutes; Includes
Unanimous Vote to Seek a 3-Year Public Probation with
Inspections (Dockets DS-03-055/PH-03-066), and to Issue
Three Advisory Letters (Dockets DS-03-036/PH-03-042; DS-
04-062/PH-04-061; and DS-03-060/PH-03-070).*

BOARD OF REGISTRATION IN PHARMACY
PHARMACY BOARD MEETING MINUTES:
TUESDAY, SEPTEMBER 21, 2004
239 CAUSEWAY STREET, ROOM
BOSTON, MASSACHUSETTS 02114

Present: Karen Ryle, R.Ph., M.S., Secy.; Harold Sparr, R.Ph.; M.S., Marilyn Barron, MSW; Steven Budish (exited at 2:50 p.m.); Donald Accetta, M.D., M.Ph. (exited at 12:00 p.m.); Joel Berman, R.Ph.; George Cayer, R.Ph.; William Gouveia, R.Ph., M.S. (exited at 12:00 p.m.); Sophia Pasedis, R.Ph.

Absent: James DeVita, R.Ph., Pres.

Staff: Charles R. Young, R.Ph., Exec. Dir.; Susan Manning, Counsel; Leo McKenna, R.Ph., Pharm.D.; CQI Surveyor, Leslie Doyle, R.Ph., Healthcare Investigator; James Emery, Healthcare Investigator; Carolyn Reid, Administrative Assistant

1. 8:30 a.m. to 10:45 a.m. - New Board Member Orientation
2. 10:45 a.m. Call To Order - Karen Ryle, Secy.
3. 10:45 a.m.-11:00 a.m.- Pending Legal - Susan Manning, Counsel

In the Matter of Erle Webber, Jr., R.Ph. - Docket No. PH-04-058
Recused: Cayer (exited room)

Board reviewed *Proposed Final Decision and Order by Default*.
Motion/Sparr to adopt proposed decision and issue Final Decision and Order revoking license pharmacist license. Second/Ryle.
Vote: Unanimous in favor.

In the Matter of Vanidy Cruz, Ph. Tech. - Docket No. PH-PT-04-017

Board reviewed *Proposed Final Decision and Order by Default*.
Motion/Sparr to adopt proposed decision and issue Final Decision and Order revoking license pharmacy technician license. Second/Gouveia.
Vote: Unanimous in favor.

In the Matters of Shoppers Drug (Docket Nos. DS-02-115; DS-03-010 and DS-03-015) and Monty Schwartz, R.Ph. (Docket Nos. PH-03-006; PH-02-022 and PH-03-026).

Board reviewed/discussed licensee's proposal for settlement of pending matters. Motion/Cayer to deny request for proposed settlement terms. Second/Sparr. Vote: Unanimous in favor.

4. October 04 meeting dates: Motion/Sparr to change meeting from October 5 to October 12. Second/Ryle. Vote: Unanimous in favor.

5. 11:00 a.m.-11:05 a.m.- Review of Minutes.
Motion/Berman to accept July 13, 2004 minutes. Second/Cayer.
Vote: Unanimous in favor.

Motion/Sparr to accept August 10, 2004 minutes. Second/Gouveia.
Vote: Unanimous in favor.

6. 11:05 a.m. to 12:00 p.m.
Investigative Conference: DS-03-037, DS-03-039 and PH-03-044.
McClelland's Home Health Pharmacy, 85 Interstate Dr., W.
Springfield, MA (Lic. No. 3054), McClelland's Drug Store, 43 Main
St., Lee, MA, (Lic. No. 2362) and Patrick Downing, R.Ph. (Registrant),
Lic. No. 21109.

Complaint alleged failure to file controlled substance loss reports in a timely manner.

CEs: compliant

Present: Registrant
David Losier, Esq.

Registrant stated that in April 2002, after becoming aware of drug losses at the Lee location, he conducted an investigation (including installation of hidden cameras) of facility and spoke with the Manager of Record (whom he had been acquainted with for a long time). When the Manager of Record admitted to an addiction, Registrant terminated his employment. Registrant acknowledged he, should have immediately reported the losses to authorities. Regarding the W. Springfield location, in October 2002, he became aware of strength changes being made to prescriptions. Registrant stated he did an

internal investigation; terminated an employee; and reported the matter to the police.

Motion/Sparr to take matter under advisement. Second/Gouveia.

Vote: Unanimous in favor.

Motion/Pasedis to issue and Advisory Letter with Registrant to terminate tenure as Manager of Record for one year. Second/Gouveia.

Oppose: Sparr, Accetta. Motion carried.

7. 12:00 p.m. to 1:15 p.m. – Lunch

8. NABP Fall Conference - Pasedis and Ryle are interested in attending.

9. 1:15 p.m. to 1:45 p.m. – Complaint Review

Leslie Doyle, Healthcare Investigator

In the matter of Barry Cadden, R.Ph. (Lic. No. 21239) and New England Compounding Center (Lic. No. 2848), 697 Waverly St., Framingham, MA (Docket Nos. PH-03-066; DS 03-055; PH 03-070; DS 03-060; DS-04-062; SA-PH-04-161 and DS-03-036 and PH 03-042)

Recused - Pasedis (exited room)

PH-03-066/DS 03-055: Motion/Sparr to issue Advisory Letter stating form is non-compliant and may not be used. Second/Cayer. Unanimous in favor.

PH-03-070/DS-03-060: Motion/Cayer to issue Advisory Letter stating terminology to be used must comply with 247 CMR. Second/Sparr. Unanimous in favor.

DS-04-062/SA-PH-04-061 Motion/Cayer to issue Advisory Letter stating marketing practices are nonconforming and must cease stating the "for use" in advertisements. Second/Berman. Unanimous in favor.

DS-03-036/PH-03-042 -Adverse Event Report.

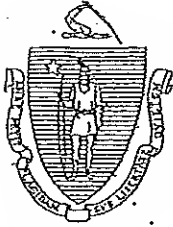
Motion/Sparr to seek Reprimand and three year probationary status with periodic inspections, two CEs in Medical Error Prevention and USP; must track all adverse event reports to be reviewed by the Board and may result in additional action. Second/Budish. Vote: Unanimous in favor.

10. 1:45 p.m. to 2:15 p.m. Investigative Conference

October 4, 2004 – Letter from Mass. Bd. Offering Consent

Decree Imposing Probation To Resolve

Dockets DS-03-055/PH-03-066



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
250 Washington Street, Boston, MA 02108-4619

MITT ROMNEY
GOVERNOR
KERRY HEALEY
LIEUTENANT GOVERNOR
RONALD PRESTON
SECRETARY
CHRISTINE C. FERGUSON
COMMISSIONER

Board of Registration in Pharmacy
239 Causeway Street, 5th Floor
Boston, MA 02114

October 04, 2004

Barry J. Cadden, R.Ph.
Manager of Record
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

RE: Docket Number DS-03-055/ PH-03-066/ New England Compounding Center (Lic. No. 2848) and Barry Cadden, R.Ph., License No. 21239

Dear Mr. Cadden:

The Board has voted to resolve the above-referenced case by offering you a consent agreement to resolve issues related to the above-referenced matter.

Please be advised that if you choose not to enter into the Agreement, the Board will proceed to a formal hearing, pursuant to G.L. c. 30A.

Please return both copies of the Agreement to the Board at your earliest convenience but no later than within ten (10) days of their receipt. The Board will then sign them and an executed copy will be returned to you.

Please contact Associate Director James D. Coffey at 617-727-6095 if you have any questions regarding this matter.

Sincerely,

Charles R. Young, R.Ph.
Executive Director
Board of Registration in Pharmacy

Enc.

By Certified Mail 7003 1010 0003 3509 7959

COMMONWEALTH OF MASSACHUSETTS

SUFFOLK COUNTY

BOARD OF REGISTRATION
IN PHARMACY

In the Matter of)
NEW ENGLAND)
COMPOUNDING CENTER)
Registration No. 2848)
BARRY J. CADDEN, R.Ph.)
License No. 21239)

DOCKET NOS. DS-03-055
PH-03-066

CONSENT AGREEMENT

The Board of Registration in Pharmacy ("Board") and NEW ENGLAND COMPOUNDING CENTER (Pharmacy Registration No. 2848), located at 697 Waverly Road, in Framingham, Massachusetts ("Registrant"), and BARRY J. CADDEN, R.Ph. ("Licensee") Pharmacist License No. 21239 and Manager of Record of Registrant, do hereby stipulate and agree that the following information shall be entered into and become a permanent part of the file of Registrant which is maintained by the Board:

1. The parties enter into this Consent Agreement ("Agreement") to resolve disputed matters arising out of the complaints pending against Registrant and Licensee, respectively, as Docket Nos. DS-03-055 and PH-03-066 ("Complaints").
2. The Registrant agrees that this Agreement has been entered into as a result of an adverse event complaint report investigated by the U.S. Food and Drug Administration alleging that Registrant, while the Licensee was Manager of Record, failed to comply with accepted standards in compounding a certain order for methyprednisolone acetate preservative free 80mg/ml suspension
3. Accordingly, the Registrant agrees to the following:
 - a. The conduct described in Paragraph 2. above constitutes professional misconduct warranting disciplinary action by the Board pursuant to G.L. c. 112, § 61 and 247

CMR 9.01(1);

- b. The Registrant and Licensee are hereby REPRIMANDED by the Board and the Registrant's pharmacy registration and Licensee's pharmacist license are hereby placed on probation for a minimum three (3) year period (the "Probationary Period"), commencing on the date this Consent Agreement is executed by the Board; and
- c. The Registrant and Licensee agrees that during the Probationary Period:
 - 1) Registrant's manager of record shall be required to develop and implement written policies and procedures to provide for and insure that USP Guidelines are followed and the Registrant performs in accordance with USP Guidelines and 247 CMR;
 - 2) Registrant's manager of record shall be required to update standard operating procedures on a quarterly basis
 - 3) Registrant may be inspected by the Board;
 - 4) Registrant will keep a written report of each adverse event reported and make such reports available for review by the Board upon request during inspections;
 - 5) Registrant will provide an after business hours telephone number for consumer use and have written protocols for after business services; and
- 4. Registrant and Licensee acknowledge that the Registrant and Licensee must apply in writing to the Board for termination of the Probationary Period and that termination of the Probationary Period shall be granted only if all of the conditions set forth above in Paragraph 3.c. have been met. The Board may request a conference to discuss the merits of such request.
- 5. This Agreement and its contents shall be incorporated into the records maintained by the Board. This Agreement and its contents are matters of public record, and are subject to disclosure without limitation to the public and equivalent state licensing boards.
- 7. The Board agrees that in return for the execution and fulfillment of the requirements of this Agreement by the Registrant and Licensee, the Board will not advance the prosecution of the Registrant and Licensee pursuant to the Complaint; any and all other rights of the Board to take action within the scope of its authority are expressly reserved.
- 8. The Registrant and Licensee understand and agree that the failure to accept the terms of this Agreement shall nullify the representations contained herein, and permit the Board to initiate formal adjudicatory action under the State Administrative Procedure Act, G.L. c. 30A, and the Standard Adjudicatory Rules of Practice and Procedure, 801 CMR 1.00 *et. seq.*
- 9. The Registrant and Licensee understand and agree that the decision to enter into this Agreement and to accept the terms and conditions herein described is a final act and is not subject to reconsideration or judicial review.

10. The Registrant and Licensee state legal counsel has been consulted in connection with the decision to enter into this Agreement and if not, that there was an opportunity to do so.
11. The Registrant and Licensee certify this document entitled "Consent Agreement" has been read. The Registrant and Licensee understand that, by executing this Agreement, the Registrant and Licensee are waiving any right to a formal hearing with rights to confront and cross-examine witnesses, to call witnesses, to present evidence, to testify on its own behalf, to contest the allegations, to present oral argument, to appeal to court in the event of an adverse ruling, and all other rights set forth in G.L. c. 30A and 801 CMR 1.01 *et seq.*

NEW ENGLAND
COMPOUNDING CENTER

By: _____
Barry J. Cadden, R.Ph.
Director of Pharmacy

Date: _____

Barry J. Cadden, R.Ph.
Manager of Record
Date: _____


BOARD OF REGISTRATION
IN PHARMACY

By: _____
James T. DeVita, R.Ph.
President

Effective Date: _____

Board Dec. No.
Cert Mail No. 7003 1010 0003 3509 7959

*November 11, 2004 Letter From NECC Asking Mass. Bd. to
Reconsider Proposed Disciplinary Action
(Dockets DS-03-055/PH-03-066)*

 Dwyer & Collora, LLP

600 Atlantic Avenue
Boston, Massachusetts 02210-2211
Telephone (617) 371-1000
Fax (617) 371-1037
www.dwyercollora.com

Paul R. Cirel
(617) 371-1025
pcirel@dwyercollora.com

November 11, 2004

Susan Manning, Esq.
The Commonwealth of Massachusetts
Board of Registration in Pharmacy
239 Causeway Street
Boston, MA 02114

Re: Docket Number DS-03-055/PH-03-066/New England Compounding
Center (Lic. No. 2848) and Barry Cadden, R.Ph. License No. 21239

Dear Ms. Manning:

On behalf of my clients, Barry Cadden, R.Ph., and New England Compounding Center ("NECC"), I am writing to respond to Mr. Young's October 4, 2004 letter regarding the above-referenced matters. Thank you for the courtesy of extending the time for this reply.

As you may be aware, NECC is now licensed in 44 states, and has applications pending in 2 others.¹ That resume speaks volumes to the quality of its products, and to its reputation. More significantly, its success in passing the due diligence inquiries and inspections that are attendant to those licenses is a testament to both NECC's and Mr. Cadden's commitment to quality assurance and regulatory compliance. Indeed, since contracting with a national expert in Aseptic Compounding (Eric Brennan) in 2002, NECC has implemented policies and procedures that address – and in some instances exceed – the proposed probationary conditions in paragraph 3.c. of Mr. Young's letter. With Mr. Brennan's guidance, NECC already has:

- Conducted an independent review and evaluation of its sterile compounding practices

¹ NECC currently does business in 4 states that do not require a license/permit: Georgia, New Jersey, Pennsylvania, Wisconsin, and plans to apply for licensure in the two remaining states: Tennessee and Arkansas.

- Developed a comprehensive set of sterile products compounding standard operating procedures.
- Implemented a comprehensive quality management program that includes:
 - Sterile products specifications.
 - Staff, facilities, and process controls.
 - Aseptic process validation.
 - Ongoing environmental bioburden monitoring.
 - Batch quality control release testing that includes pH, absence of visible foreign particulates, closure integrity, sterility and endotoxin.
 - Frequent monitoring of drug content potency.
- Implemented a formal complaint management/corrective and preventive action (CAPA) program.
- Established USP <797> gap-analysis and standards.

In addition, NECC has recently formalized a "Quality Assurance Team" which includes the director of pharmacy, the head technician, a sterile technician, the general manager and the marketing manager. The Team meets monthly with the stated mission of eliminating pharmacy error. Finally, following the suggestion in Mr. Young's letter (at paragraph 3.c.5), NECC has formalized an after business hours protocol to insure 24/7 consumer access. NECC's commitment to all these initiatives should be well known to the Board, which has inspected the facility three times since last February (twice, with a representative from the FDA):

- | | |
|----------------------|---|
| • February 20, 2004 | MA Board of Registration in Pharmacy
Ms. Leslie Doyle and Mr. James Emery |
| • September 23, 2004 | MA Board of Registration in Pharmacy
Mr. James Emery and Mr. Leon McKenna
and
FDA - [REDACTED] |
| • September 28, 2004 | MA Board of Registration in Pharmacy
Mr. James Emery and Mr. Leon McKenna
and
FDA - [REDACTED] |

All of these inspections have been without incident.

While I think it fair to say that the product of NECC's interaction with the Board — as demonstrated above — is a success story, such would not be the case if the resolution were to include a disciplinary sanction (including the reprimand proposed in Mr. Young's

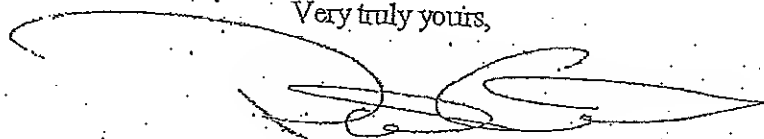
Susan Manning, Esq.
November 11, 2004
Page 3

letter). The collateral consequences to many, if not all of NECC's 42 other licenses, would be potentially fatal to the business.² Such a catastrophe is clearly not the intended result of the Board's proposed reprimand, nor is it warranted in this case. The Board's mandate is to protect the public health safety and welfare, not to punish its licensees (see, e.g., Gurry v. Board of Public Accounting 394 Mass. 118, 127-128 (1985); Levy v. Board of Registration in Medicine 378 Mass. 519, 527 (1979)).

Mr. Cadden and NECC have demonstrated their commitment to remediation, and are prepared to continue to do so. In that regard, NECC and Mr. Cadden will agree to all of the probationary terms offered in Mr. Young's letter, and will further agree to bear the burden and cost of monitoring and reporting their compliance.³ That result could be accomplished through a non-disciplinary resolution such as a continuance (pending a period of monitoring) or a "stayed probation." Whatever the vehicle, Mr. Cadden and NECC are ready, willing and able to insure all of the public protection components of Mr. Young's proposed resolution, but respectfully request that the Board do so without also imposing discipline which may destroy their business.

Both Mr. Cadden and I are available to meet with you, Mr. Young and/or the Board itself to discuss resolution of this matter. We look forward to your reply.

Very truly yours,



Paul Girel

PC/mjc

² Once disclosed, the reprimand will surely result in inquiries/investigations in those other jurisdictions. Regardless of the derivative actions taken, the attendant legal and administrative costs will be devastating.

³ NECC is prepared to extend Mr. Brennan's contract to provide ongoing monitoring - on such matters as the Board may prescribe - with regularly scheduled written reports to the Board.

*November 23, 2004 – Mass. Bd. Meeting Minutes; Includes
Unanimous Vote Denying Request to Revise Consent Decree
(Dockets DS-03-055/PH-03-066)*

BOARD OF REGISTRATION IN PHARMACY
PHARMACY BOARD MEETING MINUTES
TUESDAY, NOVEMBER 23, 2004
239 CAUSEWAY STREET, ROOM 206
BOSTON, MASSACHUSETTS 02114

Members Present: James DeVita, R.Ph., Pres.; Karen Ryle, R.Ph., M.S., Secy.; Marilyn Barron, MSW, Public Member; Joel Berman, R.Ph.; George Cayer, R.Ph.; William Gouveia, R.Ph., M.S., Sophia Pasedis, R.Ph., Pharm.D.

Members Absent: Harold Sparr, R.Ph., M.S.; Steven Budish, Public Member; Donald Accetta, M.D.

Staff Present : Charles R. Young, R.Ph., Exec. Dir.; James D. Coffey, R.Ph., Assoc. Dir.; Leo McKenna, R.Ph., Pharm.D., CQI Surveyor; Susan Manning, Board Counsel; Leslie Doyle, R.Ph., Healthcare Supervisor; James Emery, Healthcare Investigator; Samuel Penta, R.Ph., Healthcare Investigator; Carolyn Reid, Admin. Asst.

AGENDA ITEMS

1. 8:30 a.m. - Call to Order – Pres. DeVita.
2. 8:35 a.m. - Review of minutes from a previous meeting – tabled.
3. 8:40 a.m. to 9:15 a.m. - **File Review**
Office of Investigations: Investigators Doyle, Emery and Penta
4. 9:15 a.m. - **Report of Offices**
Legal: Board Counsel Susan Manning
9:20 a.m. - Motion/DeVita to enter Adjudicatory Session. Second/Ryle.
10:00 a.m. - Motion/Ryle to return to open session. Second/Cayer.
Vote: Unanimous in favor.

Robyn Kaplan-Callahan (Docket No. PH/PT-04-073)
Motion/DeVita to adopt proposed Final Decision by Default and issue order revoking pharmacy technician license. Second/Gouveia.
Vote: Unanimous in favor.

Aimee Whittington, R.Ph. (Docket No. PH-02-098/exp. 12/31/02)
Motion/Cayer vote to adopt proposed Final Decision and Order and issue
order revoking right to renew license. Second/Cayer. Vote: Unanimous in
favor.

Albert Chow, R.Ph. (Docket No. PH-03-093) Motion/Cayer grant Motion
for Reconsideration. Second/Berman. Vote: Unanimous in favor.
After review and discussion of Motion for Reconsideration filed by
Licensee, Board voted to revise Final Decision and Order dated
November 10, 2004 and issue Final Decision and Order after
Reconsideration by motion/Cayer. Second/Berman. Vote: Unanimous in
favor.

New England Compounding Center, DS-03-055
Board reviewed NECC response to proposed Consent Agreement.
Motion/DeVita to deny request to revise terms. Second/Gouveia. Vote:
Unanimous in favor.

5. 10:10 a.m. - Investigative Conference - DS-05-001 & PH-05-014
In the Matter of Brooks Pharmacy #396, 60-62 Groton St., Pepperell,
MA 01463 (Permit No. 2971) and Registrant Stefanie S. Dutton, R.Ph.
(Lic. No. 20852)

Conference reviewed complaint alleging that on or about May 03, 2004,
Registrant dispensed Chlorpropamide 100mg tablets rather than
Chlorpromazine 100mg as prescribed while employed at Brooks
Pharmacy # 396.

Present: Complainant; Registrant; Catherine Hoover, Manager of Record;
and Kevin Miller, Pharmacy Supervisor

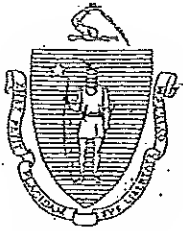
CEs: Registrant - compliant

Registrant admitted to dispensing Chlorpropamide 100mg instead of
the prescribed Chlorpromazine 100mg, stating that the medication error
occurred due to a software problem that shortened the ending of the
medication name (full name of medication did not appear on the screen)
resulting in Chlorpropam being recorded, filled and dispensed. On refill,
Registrant verified the prescription information from the original

January 11, 2006, Letter From Mass. Bd. Offering Revised

Consent Decree

(Dockets DS-03-055/PH-03-066 and DS-05-040)



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
239 Causeway Street, Boston, MA 02114

MITT ROMNEY
GOVERNOR

KERRY HEALEY
LIEUTENANT GOVERNOR

TIMOTHY R. MURPHY
SECRETARY

PAUL J. COTE, JR.
COMMISSIONER

JEAN K. PONTIKAS
DIRECTOR

Office of the General Counsel
(617) 973-0865

January 11, 2006

CERTIFIED MAIL No. 7003 2260 0007 2582 3694

Paul R. Cirel, Esq.
Dwyer & Collora, LLP
600 Atlantic Avenue
Boston, MA 02210-2211

RE: In the Matter of New England Compounding Center and Barry J. Cadden
Docket Nos. DS-03-055, PH-03-066, DS-05-040

Dear Paul,

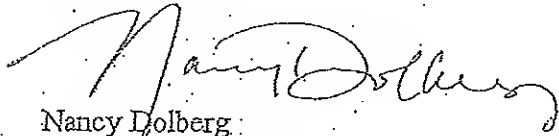
The Board of Registration in Pharmacy (Board) has now signed the Consent Agreement for Stayed Probation (Agreement) of New England Compounding Center's (NECC) Registration and Barry J. Cadden's license. NECC and Mr. Cadden have agreed to enter into the Agreement, of which an original is enclosed, with the Board in resolution of complaint Docket Nos. DS-03-055, PH-03-066 and DS-05-040. Please note carefully that the effective date of the Agreement is January 10, 2006, as is stated on the signature page of the Agreement.

NECC and Mr. Cadden are required to comply with the terms of the Agreement as of the effective date. It is their responsibility to ensure that the Board receives all required documentation and information by the due dates specified in the Agreement. All documents should be sent to Karen Fishman, Probation Monitor, Department of Public Health, Division of Health Professions Licensure, 239 Causeway Street, Boston, MA 02114. Ms. Fishman should also be contacted at (617) 973-0951 regarding any other questions you, NECC or Mr. Cadden have regarding implementation of the Agreement.

A copy of this letter and the Agreement will remain in the complaint files of the above-referenced docket numbers.

Thank you for your courtesy and cooperation in this matter.

Sincerely,

A handwritten signature in cursive script, appearing to read "Nancy Dolberg". The signature is written in dark ink and is positioned above the printed name and title.

Nancy Dolberg
Prosecuting Counsel

cc: Karen Fishman

COMMONWEALTH OF MASSACHUSETTS

SUFFOLK COUNTY

BOARD OF REGISTRATION
IN PHARMACY

In the Matter of
NEW ENGLAND
COMPOUNDING CENTER
Registration No. 2848
BARRY J. CADDEN, R.Ph.
License No. 21239

Docket Nos. DS-03-055
PH-03-066
DS-05-040

CONSENT AGREEMENT

The Board of Registration in Pharmacy ("Board") and NEW ENGLAND COMPOUNDING CENTER ("NECC") (Pharmacy Registration No. 2848), located at 697 Waverly Road, in Framingham, Massachusetts ("Registrant"), and BARRY J. CADDEN, R.Ph. ("Licensee") Pharmacist License No. 21239 and Manager of Record of Registrant, do hereby stipulate and agree that the following information shall be entered into and become a permanent part of the files of Registrant and Licensee which are maintained by the Board:

1. The parties enter into this Consent Agreement ("Agreement") to resolve disputed matters arising out of the complaints pending against Registrant and Licensee, respectively, as Docket Nos. DS-03-055, PH-03-066 and DS-05-040 ("Complaints").
2. The Registrant, Licensee and the Board stipulate and agree that this Agreement is in settlement of complaints relating to an adverse event complaint report investigated by the United States Food and Drug Administration for methyprednisolone acetate preservative free 80 mg/ml suspension, and concerning the dispensing of Trypan Blue without a valid prescription ("the Complaints").
3. The Registrant, Licensee and the Board acknowledge that this Agreement is a nondisciplinary agreement not reported to the National Association of State Boards of Pharmacy or other outside report agencies, except that the Licensee's failure to fulfill the requirements of paragraph 5 may result in the imposition of discipline by the Board.
4. In order to resolve these matters without further proceedings before the Board, the Registrant, the Licensee, and the Board agree that on the date of the execution of this Agreement by the Board ("Effective Date") the Board will order that the Licensee be placed on Probation for a Period of One (1) Year, and the probation order will be

Stayed for one (1) year from the Effective Date of this Agreement ("the Stay").

5. The Registrant and the Licensee agree as follows:

(a) Within 45 days from the Effective Date of this Agreement, the Registrant and Licensee shall provide documentation satisfactory to the Board that Board-approved evaluator: Pharmacy Support, Inc. ("PSI" or "Evaluator"), at the expense of the Registrant and Licensee, has conducted an inspection of and prepared a written report analyzing Registrant's compounding practices and compliance with United States Pharmacopeia Standard 795 - Non-Sterile Compounding Procedures and USP Standard 797 - Sterile Compounding Procedures, in accordance with 247 CMR 9.01(3) ("USP Standards"), with any recommendations for revisions to practice for compliance with USP Standards ("the First Report"). The inspection shall include consideration of, but not be limited to:

- i. Sterile Environmental Design
- ii. Quality Assurance Program
- iii. Media Fills (operator qualification/process validation)
- iv. Environmental Monitoring
- v. Cleaning and Sanitizing Program
- vi. Training Records
- vii. Process Control
- viii. Equipment
- ix. Finished Preparation Testing
- x. Adverse Event Records

(b) The Registrant and Licensee will arrange for the Evaluator to provide a copy of the First Report as described in Paragraph 5(a) directly to the Board within fourteen days of the inspection.

(c) The Registrant and Licensee will implement all recommendations made by the Evaluator within 90 days of the Effective Date of this Agreement. The Registrant and Licensee must petition and receive the approval of the Board to exempt or postpone implementation of any particular recommendation.

(d) Within six months of the Effective Date of this Agreement, the Registrant and Licensee shall provide documentation satisfactory to the Board that the Evaluator, at the expense of the Registrant and Licensee, has conducted a second inspection of Registrant and prepared a written report after an analysis as described in Paragraph (5) above, and further, as to whether the recommendations made by the Evaluator in the First Report have been implemented ("the Second Report").

(e) The Registrant and Licensee will arrange for the Evaluator to provide a copy of the Second Report as described in Paragraph 5(d) directly to the Board within fourteen days of the inspection.

(f) The Registrant and Licensee will update Standard Operating Procedures on a biannual

basis.

(g) The Registrant and Licensee will keep a written report of each adverse event reported and make such reports available for review by the Board upon request.

6. If the Registrant and Licensee successfully complete the requirements of paragraph 5, its registration and his license will not be placed on probation.
7. If the Registrant and the Licensee fail to successfully complete the requirements of paragraph 5, the Stay will be withdrawn by the Board and the Board's order of Probation for a Period of One (1) Year ("Probation") will be imposed upon the Registrant and Licensee without the necessity of additional proceedings pursuant to G.L. c. 30A. The terms and conditions of Probation will be determined by the Board at that time and may include, but not be limited to practice restrictions, monitoring conditions, appearances before the Board, and continuing education and training.
8. This Agreement and its contents shall be incorporated into the records maintained by the Board. This Agreement and its contents are matters of public record, and are subject to disclosure without limitation to the public and equivalent state licensing boards.
9. The Board agrees that in return for the execution and fulfillment of the requirements of this Agreement by the Registrant and Licensee, the Board will not advance the prosecution of the Registrant and Licensee pursuant to the Complaints; any and all other rights of the Board to take action within the scope of its authority are expressly reserved.
10. The Registrant and Licensee understand and agree that the failure to accept the terms of this Agreement shall nullify the representations contained herein, and permit the Board to initiate formal adjudicatory action under the State Administrative Procedure Act, G.L. c. 30A, and the Standard Adjudicatory Rules of Practice and Procedure, 801 CMR 1.00 *et seq.*
11. The Registrant and Licensee understand and agree that the decision to enter into this Agreement and to accept the terms and conditions herein described is a final act and is not subject to reconsideration or judicial review.
12. The Registrant and Licensee state legal counsel has been consulted in connection with the decision to enter into this Agreement and if not, that there was an opportunity to do so.
13. The Registrant and Licensee certify this document entitled "Consent Agreement" has been read. The Registrant and Licensee understand that, by executing this Agreement, the Registrant and Licensee are waiving any right to a formal hearing with rights to confront and cross-examine witnesses, to call witnesses, to present evidence, to testify on its own behalf, to contest the allegations, to present oral argument, to appeal to court in the event of an adverse ruling, and all other rights set forth in G.L. c. 30A and 801 CMR 1.01 *et seq.*

NEW ENGLAND
COMPOUNDING CENTER

By: Barry J. Cadden
Barry J. Cadden, R.Ph.
Director of Pharmacy

Date: 1/5/06

Barry J. Cadden
Barry J. Cadden, R.Ph.
Manager of Record
Date: 1/5/06

BOARD OF REGISTRATION
IN PHARMACY

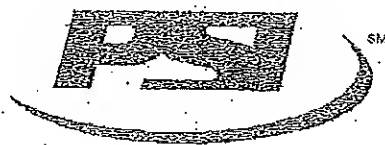
By: Karen Ryle
Karen Ryle, R.Ph., M.S.
President

Effective Date: 1/10/06

Board Dec. No. 1210, 1211
Cert Mail No.



April 7, 2006 - Final Report from PSI
(Dockets DS-03-055/PH-03-066 and DS-05-040)



**Final Report
USP <795>/<797> Implementation
New England Compounding Center
Framingham, Ma**

Background

Pharmacy Support, Inc. (PSI) has been contracted by New England Compounding Center (NECC) located at 697 Waverly Road, Framingham, MA, to develop and implement a plan for compliance to requirements set forth in USP <795> and <797>. The Board Registration in Pharmacy for the commonwealth of Massachusetts in a consent decree memo dated January 10, 2006 named Pharmacy Support, Inc. as the authorized third party reviewer. The consent decree was addressed to Mr. Barry J. Cadden, R.Ph, Manager of Record of Registrant.

The chronology of events is as follows:

- Consent decree signed and agreed upon: January 10, 2006
- Audit of NECC by PSI: January 17 and 18, 2006
- Audit report issued: January 26, 2006
- Initial draft of Standard Operating Procedures sent to NECC for review and comment: February 3 through February 16, 2006
- Phase I implementation and initial training: March 7 – 9, 2006
- Interim Report Issued: March 22, 2006
- Phase II implementation and on-going training: March 27 – 31, 2006
- Final Report Issue: April 7, 2006

Conclusion

New England Compounding Center has made significant improvements over the past several months. They have demonstrated the ability to be compliant with all state and federal regulations. They have appropriate equipment, procedures, basic facility design and environment controls. The non-sterile preparations area is noticeably cleaner and more organized. As of the date of this report, it is the opinion of our firm that in order for NECC to be in substantial compliance the follow must occur.

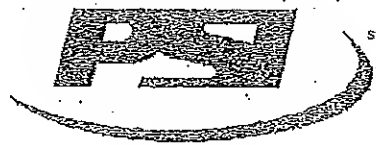
Redesign of clean room 1 where sterile preparations are compounded
(Floor, Ceiling, and HVAC)

Proper utilization of clean room 2 with respect to process/people flow
(one-way flow only)

Removal of non-essential equipment in clean room 2.
(microwave, dishwasher, autoclave, printers, etc)

Consideration for different clean room gowns and gloves or use of sterile sleeves over gown to assure wrists and arms are always covered.

Sterilizing filters used to filter sterilize preparations should be integrity tested.



Final Report
USP <795>/<797> Implementation
New England Compounding Center
Framingham, Ma

The Pharmacist In charge has committed to these enhancements and has put an action plan in place to assure compliance.

PSI is satisfied with the progress to date and is confident that the remaining issues will be resolved in a short period of time.

Purpose

The purpose of this report is to detail the implementation process and document the results. An interim report was issued to NECC at the completion of phase 1. This report will summarize the overall results of phase one, but will not restate each issue or recommendation identified at that time. Recommendations not completed as identified in the audit report or the interim report will be outlined in this report. Recommendations are those items not specifically stated in the USP, but were recommended as good compounded practices and are supported by sound scientific judgment and are considered routine industry practice.

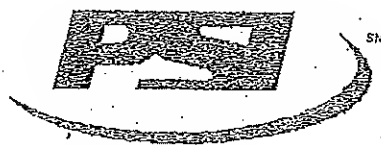
Results of Implementation Plan

Initial Audit

All compounding process elements were evaluated during the audit in January. Process elements included people, equipment, environment, materials, measures and methods. Critical control points for each element was considered from a risk perspective and reviewed accordingly.

An audit report was prepared at the completion of the audit. The report was provided to NECC and a copy was sent to the State Board of Pharmacy. A corrective action plan was discussed. NECC was responsible for completing all corrective actions. A list of recommendation was also included. PSI provided technical and quality support during this phase. Many of the action items required a Standard Operating Procedure (SOP) be written. PSI assumed the responsibility of writing all SOP's. The SOP's were written as baseline documents with the intention of customizing the procedures during the next phase of implementation. Customization would add "how to" instructions specific to their facility, equipment, environment, etc. A follow-up date for the next visit was established.

The audit report recommended that NECC hire a professional Quality Assurance associate who would develop and take ownership of the quality systems. A quality system brings the process elements together for the common purpose of business, service, quality, environment, safety and efficacy. NECC has promoted an employee to assume this role. This employee, however, has no



Final Report
USP <795>/<797> Implementation
New England Compounding Center
Framingham, Ma

experience in the quality assurance field and will require formal training to effectively make the process elements and control systems efficient and effectively make recommendations for continual quality improvements. He will also require formal training in auditing to assure the facility is maintained in a substantial state of regulatory compliance for local, state and federal requirements.

Initial Draft of Sop's

PSI authored approximately 42 Standard Operation Procedures covering requirements in USP <795> and <797>. SOPs were written for the following categories:

- Guidelines for Compounded Preparations
- Personnel
- Facilities and Cleaning Procedures
- Pharmacy Practices
- Compounding Preparations
- Cytotoxic and/or Hazardous Drugs
- Sterilization and Depyrogenation
- Quality Assurance/Quality Control

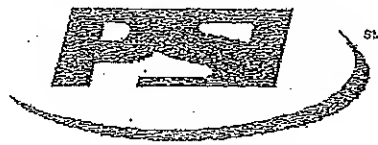
All draft SOP's were forwarded to NECC for review and comment. The review and comment phase was completed within a few weeks. SOP's for equipment and supplies were written during the following phase as equipment manuals were provided and equipment qualification were completed.

Implementation of SOP's and Initial Training

Several tasks were completed during our visit in March 8, 9, and 10, 2006.

Several training sessions were conducted.

- Aseptic Technique
- Basic Microbiology
- USP <795> <797> Requirements
- Good Documentation Practices
- Out of Specification (OOS) Process
- Complaint Handling System
- Quality Assurance Systems/program
- Procedure Management
- Change Control



Final Report
USP <795>/<797> Implementation
New England Compounding Center
Framingham, Ma

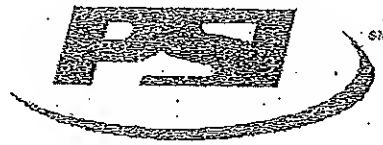
Class sessions were conducted in a classroom environment utilizing power point presentations and handouts. In some cases, quizzes were presented at the end of the session to assure a basic understanding of the concepts was obtained. The employee selection for attendance for each session was at the discretion of the Pharmacist in Charge. All training was documented and is on file at NECC.

All temperature controlled equipment, i.e. refrigerators, freezers, autoclaves, etc. were qualified using validated temperature mapping equipment. The purpose of the qualification was to determine if the equipment was capable of maintaining temperatures and operates as expected. The results were documented in a report and sent as an attachment to the Interim report. One freezer (serial #) and the depyrogenation oven (serial #) did not operate as expected and new equipment was purchased.

Viable and non-viable environmental monitoring samples for both surface and air were taken by PSI and sent to PSI laboratory for analysis. The quantity and location of each sample was defined in the draft SOP. Identification and enumeration was performed on all samples at PSI. Isolates identified at the critical locations were further identified and documented. Results of all sampling were included in the interim report. As experts in the field of microbiology, our interpretation of the results was less than desirable, and we encouraged the facility to attend another training session for aseptic processing and to evaluate their cleaning procedures.

All draft SOP's were in the approval routing process during this time. All recommended changes requested from NECC were considered and changes were made when appropriate. The approval routing process includes a requirement that each employee read and understand the requirements of the procedure. Read and Understand memos for each procedure with employees' signatures is on file in the Quality department. All 42 SOP's were approved and issued during this time frame.

Also, during our visit a list of additional recommendations was compiled. This list along with observations/recommendations that were documented during the audit would be verified for completion during phase II.



**Final Report
USP <795>/<797> Implementation
New England Compounding Center
Framingham, Ma**

Interim Report

An interim report was provided to NECC on March 22, 2006. The interim report detailed the progress to date. In the interim report, it was concluded that the facility was not in substantial compliance with the USP requirements, and a plan going forward to achieve compliance was outlined. As indicated above, an additional list of recommendations was generated and discussed with the pharmacist in charge. This list was included in the interim report with plans to follow up during our next visit.

Phase II implementation and on-going training.

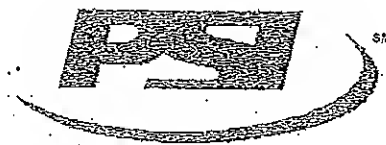
During the week of March 27, the final phase of implementation was executed. Observation of aseptic technique was observed continually during the week, with comments provided to the staff in real time.

Several of the approved SOP's were verified for compliance to the written requirements included verification of proper documentation. Several additional changes to procedures were required. Ten (10) change controls were initiated and approved during this time frame.

In addition, equipment manuals were now available and 11 more "Equipment and Supplies" SOP's were authored by PSI and processed through the approval routing system. All equipment was tagged with equipment numbers, LUMAC's (Log of Use, Maintenance And Cleaning) were assigned and implemented. All equipment requiring calibrations (thermometers, etc) have been calibrated and identified with the current status. A matrix of all calibrated equipment has been generated for managing the calibration process and assures that equipment remains in a current calibration state.

The list of observations and recommendations from the previous audit and the list of recommendations attached to the interim report were verified for completion. At the time of this report, several items have not been completed, however expected completion dates has been assigned.

Two new pieces of equipment were qualified; one (1) freezer and one (1) depyrogenation oven. Cycle development was completed and loading patterns were established for the depyrogenation oven. Results of the qualifications are documented and are being sent under separate cover.



Final Report
USP <795>/<797> Implementation
New England Compounding Center
Framingham, Ma

Additional training was conducted in Aseptic Processing Techniques for employees who compound sterile preparations. Training in Good Documentation Practices was requested and provided to employees who compound non-sterile preparations. Training was conducted in the operation and maintenance of the new depyrogenation oven. Training was provided on a continual basis to [REDACTED]. As [REDACTED] has no previous experience or formal training or education in this field, it is highly recommended that he immediately begins training in this area. All training has been documented and is in the employee training records in the quality department.

Additional Environmental Samples were collected to assure that cleaning procedures were effective, locations of samples appropriate and aseptic process techniques have improved. Samples were sent to PSI laboratories for analysis. Sample results showed significant improvement over the samples taken during our previous visit. Results of the environmental samples are documented in a report and are being sent under separate cover.

One sample in the isolator antechamber (ISO class 7) did not meet specification (positive growth) during the week. The isolator was immediately taken out of service and an investigation was initiated. On-going training for performing investigations and root cause analysis for an OOS associated with environmental monitoring was conducted with the quality manager. Additional sampling was recommended and a probable root cause was identified. Appropriate changes were immediately incorporated and a recommendation for continual monitoring was made. PSI will be available for continual technical support during this time period.

Follow-On

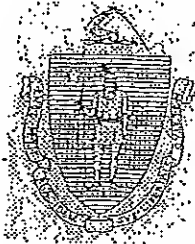
As directed by the State Board of Pharmacy a follow up audit must be conducted within six (6) months of the effective date of the consent decree. Specific dates for the audit will be determined and agreed upon by the Pharmacist in charge and PSI.

Report Prepared by:
M. Moriva
VP Quality Operations
Pharmaceutical Systems, Inc.

Moriva (Print) Moriva

Cc: C. Long – Massachusetts State Board of Pharmacy

*April 12, 2006 – Letter From Mass. Bd. to NECC, Closing
Dockets DS-03-055/PH-03-066 and DS-05-040*



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The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Division of Health Professions Licensure

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SECRETARY

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COMMISSIONER

Board of Registration in Pharmacy
239 Causeway Street, Suite 200, 2nd Floor
Boston, MA 02114
(800) 414-0168
<http://www.mass.gov/reg/boards/ph>

April 12, 2006

Barry J. Cadden, R.Ph.
NEW ENGLAND COMPOUNDING CENTER
697 Waverly Road
Frammingham, MA 01702

BY FAX and First Class Mail

Re: Pharmacy Support, Inc. (PSI) *Final Report* dated April 7, 2006
Complaint Docket Nos. DS-03-055, PH-03-066 and DS-05-040
Consent Agreement (Eff. Date: January 10, 2006)

Dear Mr. Cadden:

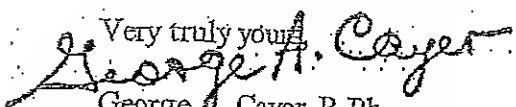
The Board of Registration in Pharmacy has reviewed the above referenced PSI Final Report (Report) provided in accordance with the terms of the Consent Agreement that New England Compounding Center (NECC) and the Board executed in resolution of the above matters.

As you are aware, PSI states that NECC has made significant improvements over the past months and demonstrated the ability to be compliant with state and federal regulations. The Board commends NECC on the progress to date.

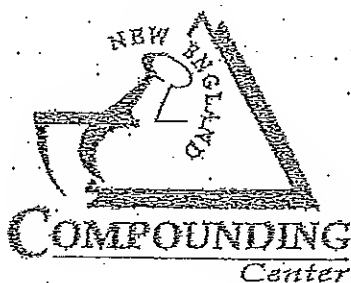
With respect to the items PSI lists in the "Conclusion" section on Page One of the Report, please advise the Board in writing regarding NECC's intentions as to the five items PSI specifically identifies in the Conclusion, with related projected timelines for completion.

Your response is requested to be provided to the Board by April 26, 2006.

Very truly yours,


George A. Cayer, R.Ph.
President

cc: Paul Cirek, Esq. BY FAX and First Class Mail



New England Compounding Center

Customized Pharmacy Services

697 Waverly Street, Framingham, MA 01702

Tel: 800.994.6322 or 508.820.0606

Fax: 888.820.0583 or 508.820.1616

www.necctx.com mail@necctx.com

Received

April 19, 2006

APR 21 2006

Mr. George A. Cayer, R.Ph., President
Massachusetts Board of Registration in Pharmacy
239 Causeway Street, Suite 200, 2nd Floor.
Boston, MA 02114

BOARD OF
PHARMACY

Re: Pharmacy Support, Inc. (PSI) Final Report dated April 7, 2006
Complaint Docket Nos. DS-03-055, PH-03-066 and DS-05-040
Consent Agreement (Eff. Date: January 10, 2006)

Dear Mr. Cayer,

I am in receipt of your letter dated April 12, 2006. Thank you for your kind words regarding our progress to date. I am pleased to offer our response regarding NECC's intentions as to the five items PSI specifically identifies in the Conclusion section on Page One of their Final Report to the Massachusetts Board of Registration in Pharmacy, dated April 2, 2006.

The items are as follows:

1. *Redesign of clean room 1 where sterile preparations are compounded (Floor, Ceiling and HVAC)*

It should first be noted that all sterile preparations are compounded within Class 10 Microenvironments, within "clean room 1." The room is not maintained as a certified clean room, nor was it ever our intent.

The ability to clean the floor under and behind our class 10 microenvironments was an issue. On April 18th, the two microenvironments were moved away from the wall and the floor shall was cleaned and sealed again in those areas. The cleaning contractor has been instructed to implement this procedure each time the floor in those areas is cleaned.

The ceiling tiles in that room are, in fact, clean room tiles.

The HVAC unit in that room will be improved per PSI's suggestions. The work has been scheduled with Victory HVAC, our certified HVAC contractor, and is expected to be completed by May 18, 2006.

2. *Proper utilization of clean room 2 with respect to process/people flow (one-way flow only).*

PSI had recommended a one way flow with personnel coming into the clean room through the personnel anteroom, but leaving the clean room directly through an emergency exit into the office

area surrounding the clean room. We do not believe this to be wise, as opening the emergency exit repeatedly during each day may result in the possibility of outside air directly flowing into the clean room. I believe that the personnel flow per the room's original design should be maintained.

3. *Removal of non-essential equipment in clean room 2 (microwave, dishwasher, autoclave, printers, etc.)*

It should first be noted that all sterile preparations are compounded within Class 10 Microenvironments, within clean room 2. Although the room is maintained as a certified clean room, we continue to only perform sterile preparations within the Class 10 Microenvironments within the room. The room was always intended to provide a bonus level of ISO 7 cleanliness around the ISO 5 Microenvironments. In addition, the equipment in question is essential for us to properly prepare compounded medications. Lastly, we perform ongoing environmental testing throughout clean room 2, including around the equipment in question, and all results have been within the proper range. I believe that maintaining the equipment necessary to properly perform our compounding operations in their current location, per the room's original design, will lead to enhanced public health, welfare and safety.

4. *Consideration for different clean room gowns and gloves or use of sterile sleeves over gown to assure wrists and arms are always covered.*

New gowns and/or gowning sleeves have been sourced and ordered and are expected to arrive this week. All pharmacists and technicians requiring these gowns/sleeves in order to assure that their wrists and arms are always covered will be trained on the proper use of the new gowns/sleeves and begin using them on or before April 30, 2006.

5. *Sterilizing filters used to filter sterilize preparations should be integrity tested.*

We order the sterilizing filters from industry leader, Millipore Corporation. We have asked Millipore to provide testing certification documentation for each lot ordered. These certificates shall be kept on file. In addition, upon receipt of each future lot of filters, we shall also begin testing one randomly selected filter and shall keep the results on file. This new testing procedure will be effective with the next lot ordered from Millipore.

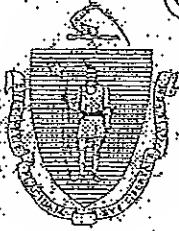
I may be reached at 508-820-0606 should you require further information.

Sincerely,

NEW ENGLAND COMPOUNDING CENTER



Barry J. Cadden, R.Ph.
Director of Pharmacy



COPY

The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Division of Health Professions Licensure

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Board of Registration in Pharmacy
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Boston, MA 02114
(800) 414-0168
<http://www.mass.gov/reg/boards/ph>

May 10, 2006

Barry J. Cadden, R.Ph.
NEW ENGLAND COMPOUNDING CENTER
697 Waverly Road
Framingham, MA 01702

Re: Consent Agreement (Eff. Date: January 10, 2006)
Complaint Docket Nos. DS-03-055, PH-03-066 and DS-05-040

Dear Mr. Cadden:

The Board of Registration in Pharmacy has reviewed your letter dated April 19, 2006 concerning certain items identified in the PSI Final Report dated April 7, 2006.

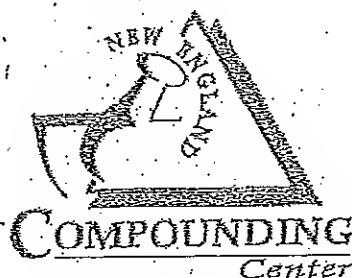
The Board seeks written confirmation of: (1) HVAC work completion; (2) receipt and proper use of gowns and sleeves; and (3) performance of random testing of sterilizing filters.

Please provide confirmation to the Board by May 22, 2006.

Very truly yours,

George A. Cayer
George A. Cayer, R.Ph.
President

cc: Paul Cirel, Esq.
DWYER & COLLORA, LLP
600 Atlantic Ave.
Boston, MA 02210-2111



New England Compounding Center

Customized Pharmacy Services

697 Waverly Street, Framingham, MA 01702

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Fax: 888.820.0583 or 508.820.1616

www.necctx.com

mail@necctx.com

Received

May 22, 2006

MAY 24 2006

Mr. George Cayet, R.Ph.
President
Massachusetts Board of Registration in Pharmacy
239 Causeway Street, Suite 200, 2nd Floor
Boston, MA 02114

BOARD OF
PHARMACY

Dear Mr. Cayet,

In response to your letter dated May 10, 2006, I am pleased to report that the following actions have been completed:

- 1) The HVAC work has been performed;
- 2) We have received and are now using the suggested gowns and sleeves;
- 3) We are now randomly testing the Millipore sterilizing filters.

Should you require further information, I may be reached at (508) 820-0606 x630.

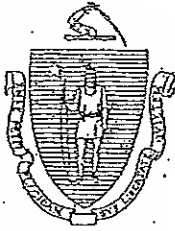
Sincerely,

NEW ENGLAND COMPOUNDING CENTER

Barry J. Caeden, RPh
Director of Pharmacy

April 12, 2006 – Letter From Mass. Bd. To NECC, Closing

Dockets DS-03-055/PH-03-066 and DS-05-040



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Division of Health Professions Licensure

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JEAN K. PONTIKAS
DIRECTOR

Board of Registration in Pharmacy
239 Causeway Street, Suite 200, 2nd Floor
Boston, MA 02114
(800) 414-0168
<http://www.mass.gov/reg/boards/ph>

June 2, 2006

Barry J. Cadden, R.Ph.
NEW ENGLAND COMPOUNDING CENTER
697 Waverly Road
Framingham, MA 01702

Re: Consent Agreement (Effective Date: January 10, 2006)
Complaint Docket Nos. DS-03-055, PH-03-066 and DS-05-040

Dear Mr. Cadden:

Please be advised that on May 23, 2006 the Board of Registration in Pharmacy reviewed your letter dated May 22, 2006 concerning follow up actions related to the PSI Final Report dated April 7, 2006 and the above-referenced Consent Agreement.

The Board voted to advise you that NECC has satisfactorily completed the terms and conditions in the Consent Agreement; including Sections a. through e. of Paragraph 5 of the Agreement. Please note that the Sections f. and g. of Paragraph 5. of the Agreement remain in effect.

If additional information is necessary, please contact Exec. Dir. Charles Young at (617) 973-0955 and or Assoc. Dir. James D. Coffey at (617) 973-0950.

Sincerely,

George A. Cayer, R.Ph.
President

cc: Karen Fishman, DHPL Compliance Officer

*September 30, 2004, Advisory Letters to NECC from Mass. Bd.
(Dockets: DS-03-036/PH-03-042; DS-04-062/PH-04-061; and
DS-03-060/PH-03-070)*



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
250 Washington Street, Boston, MA 02108-4619

Board of Registration in Pharmacy
239 Causeway Street, 5th Floor
Boston, MA 02114

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LIEUTENANT GOVERNOR
RONALD PRESTON
SECRETARY
CHRISTINE C. FERGUSON
COMMISSIONER

September 30, 2004

Barry Cadden, R.Ph.
Manager of Record
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

Re: In the Matter of:
In the matter of DS-03-036 and PH-03-042 - New England Compounding Center
(Permit # 2848).

Dear Mr. Cadden:

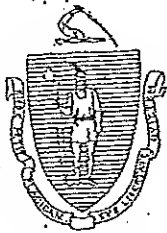
~~The Board has voted to resolve the above referenced cases by means of issuing~~
an Advisory Letter to you and New England Compounding Center. Enclosed for your
record is a copy of the final decision letter in the above referenced matter.

Please contact me at (617) 727-6095 if you have any questions regarding this matter.

Sincerely,

Charles R. Young, R.Ph.
Executive Director
Massachusetts Board of Registration in Pharmacy
239 Causeway Street, Suite 5
Boston, MA 02114

Enclosure: Advisory Dismissal Letter
Dated: September 30, 2004
Board Decision ID Number:



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health

MITT ROMNEY
GOVERNOR
KERRY HEALEY
LIEUTENANT GOVERNOR
RONALD PRESTON
SECRETARY
CHRISTINE C. FERGUSON
COMMISSIONER

Board of Registration in Pharmacy
239 Causeway Street, 5th Floor
Boston, MA 02114
(617) 727-9953

In the Matter of:
New England Compounding
Center
697 Waverly Street
Framingham, MA 01702
Registration No. 2848.
& Barry Cadden, R.Ph.
License No. 21239

Docket No. DS-03-036
PH-03-042

ADVISORY LETTER

The Board of Registration in Pharmacy ("Board") received reports from a surgical center in Rapid City, SD expressing concern about products being solicited by Barry Cadden, R.Ph., License No. 21239 ("Registrant") and New England Compounding Center, License No. 2848 (the Pharmacy). The investigation revealed that the solicitations were out of state prescriptions for office use and using a form unapproved by the Department of Public Health and Board.

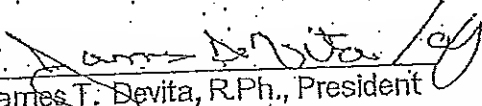
The Board has carefully reviewed the investigative reports and other information provided by the parties regarding the Complaint. The Board determined on September 21, 2004, the Complaint should be resolved by the issuance of this Advisory Letter regarding the filling of the prescription in this matter. Although an Advisory Letter does not constitute disciplinary action, this letter does communicate the Board's concern regarding the conduct that was the basis for the Complaint. The Board expects a dedicated company response and employee counseling where appropriate to insure that the factors contributing to the complaints are identified and that appropriate quality assurance measures are implemented to reduce the risk of recurrence of this type of incident.

The Board also determined that to close this matter without formal disciplinary action, the Pharmacy must within thirty days of the date of this letter cease using the

"purported prescription form", as it is not compliant with 105CMR § 721.030 et seq and G.L. c. 112 § 12D.

Please be advised that any failure of the Pharmacy to comply with any of the terms or conditions of this Advisory Letter may be a basis for the Board to reconsider this matter and reopen the Complaint.

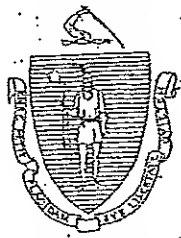
BOARD OF REGISTRATION IN PHARMACY


James T. Devita, R.Ph., President

Date: September 30, 2004

cc: Complainant

Board Dec. No.



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
250 Washington Street, Boston, MA 02108-4619

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CHRISTINE C. FERGUSON
COMMISSIONER

Board of Registration in Pharmacy
239 Causeway Street, 5th Floor
Boston, MA 02114

September 30, 2004

Barry Cadden, R.Ph.
Manager of Record
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

Re: In the Matter of:
In the matter of DS-03-060 and PH-03-070 -- New England Compounding Center
(Permit # 2848).

Dear Mr. Cadden:

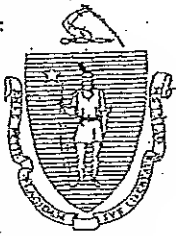
The Board has voted to resolve the above-referenced cases by means of issuing
an Advisory Letter to you and New England Compounding Center. Enclosed for your
record is a copy of the final decision letter in the above referenced matter.

Please contact me at (617) 727-6095 if you have any questions regarding this matter.

Sincerely,

Charles R. Young, R.Ph.
Executive Director
Massachusetts Board of Registration in Pharmacy
239 Causeway Street, Suite 5
Boston, MA 02114

Enclosure: Advisory Dismissal Letter
Dated: September 30, 2004
Board Decision ID Number:



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health

MITT ROMNEY
GOVERNOR
KERRY HEALEY
LIEUTENANT GOVERNOR
RONALD PRESTON
SECRETARY
CHRISTINE C. FERGUSON
COMMISSIONER

Board of Registration in Pharmacy
239 Causeway Street, 5th Floor
Boston, MA 02114
(617) 727-9953

In the Matter of:
New England Compounding
Center
697 Waverly Street
Framingham, MA 01702
Registration No. 2848
& Barry Cadden, R.Ph.
License No. 21239

Docket No. DS-03-060
PH-03-070

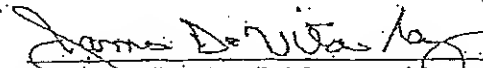
ADVISORY LETTER

The Board of Registration in Pharmacy ("Board") received a complaint from a concerned Texas pharmacist about products being solicited by Barry Cadden, R.Ph., License No. 21239 ("Registrant") and New England Compounding Center, License No. 2848 (the Pharmacy). The investigation revealed that the solicitations were offering intravitreal triamcinolone acetate and included promotional material and terminology in the advertisements.

The Board has carefully reviewed the investigative reports and other information provided by the parties regarding the Complaint. The Board determined on September 21, 2004, the Complaint should be resolved by the issuance of this Advisory Letter regarding the advertising and solicitation of this product. Although an Advisory Letter does not constitute disciplinary action, this letter does communicate the Board's concern regarding the conduct that was the basis for the Complaint. The Board expects a dedicated company response to insure that the factors contributing to the complaints are identified and that appropriate quality assurance measures are implemented to reduce the risk of recurrence of this type of incident.

Please be advised that any failure of the Pharmacy to comply with any of the terms or conditions of this Advisory Letter may be a basis for the Board to reconsider this matter and reopen the Complaint.

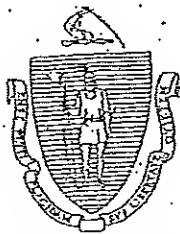
BOARD OF REGISTRATION IN PHARMACY


James T. Devita, R.Ph., President

Date: September 30, 2004

cc: Complainant

Board Dec. No.



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health

MITT ROMNEY
GOVERNOR

KERRY HEALEY
LIEUTENANT GOVERNOR

RONALD PRESTON
SECRETARY

CHRISTINE C. FERGUSON
COMMISSIONER

Board of Registration in Pharmacy
239 Causeway Street, 5th Floor
Boston, MA 02114
(617) 727-9953

In the Matter of:
New England Compounding
Center
697 Waverly Street
Framingham, MA 01072
Registration No. 2848
& Barry Cadden, R.Ph.
License No. 21239

Docket No. DS-04-062
SA-04-161

ADVISORY LETTER

The Board of Registration in Pharmacy ("Board") received complaints from an Iowa pharmacist and Wisconsin Pharmacist alleging that Barry Cadden, R.Ph., License No. 21239 ("Registrant") and New England Compounding Center, License No. 2848 (the Pharmacy) were soliciting out of state prescriptions for office use and using a form unapproved by the Department of Public Health and Board.

The Board has carefully reviewed the investigative reports and other information provided by the parties regarding the Complaint. The Board determined on September 21, 2004, the Complaint should be resolved by the issuance of this Advisory Letter regarding the filling of the prescription in this matter. Although an Advisory Letter does not constitute disciplinary action, this letter does communicate the Board's concern regarding the conduct that was the basis for the Complaint. The Board expects a dedicated company response and employee counseling where appropriate to insure that the factors contributing to the complaints are identified and that appropriate quality assurance measures are implemented to reduce the risk of recurrence of this type of incident.

The Board also determined that to close this matter without formal disciplinary action, the Pharmacy must within thirty days of the date of this letter cease using the

"purported prescription form", as it is not compliant with 105CMR § 721.030 et seq and G.L. c. 112 § 12D.

Please be advised that any failure of the Pharmacy to comply with any of the terms or conditions of this Advisory Letter may be a basis for the Board to reconsider this matter and reopen the Complaint.

BOARD OF REGISTRATION IN PHARMACY


James T. Devita, R.Ph., President

Date: September 30, 2004

cc: Complainant

Board Dec. No.

April 27, 2004, Complaint to Mass. Bd. Regarding NECC

Manufacturing an Unapproved Antiseptic Cream

(Dockets: DS-05-040/PH-05-066)



DEPARTMENT OF PUBLIC HEALTH
DIVISION OF HEALTH PROFESSIONS LICENSURE
617-727-6091

<http://www.mass.gov/dph/boards/>

APR 3 2002

Received (stamp):

Entered into the Database (Date):

Docket #:

Acknowledgment letter sent (Date):

Signature:

Please complete this form as fully as possible. (PLEASE DO NOT WRITE ABOVE LINE) Please type or print legibly in ink.
COMPLAINT BY:

Name:

[Redacted]

First Name

[Redacted]

MI

Address:

[Redacted]

Daytime Phone

Number Street

[Redacted]

City

State Zip Code

Evening Phone

Best way to reach you: Evening Phone ☒ Daytime Phone ☒ or

or

or

or

COMPLAINT AGAINST (use separate form for each licensed individual):

Name:

[Redacted]

First Name

[Redacted]

MI

Address:

697 Waverly St.

800-994-6322

Number Street

Daytime Phone

Frammingham

Ma 01702

City

State Zip Code

License Number/Type Class

New England Compounding Center

Business Name

697 Waverly St

800-994-6322

Business Address

Daytime Phone

Frammingham

Ma 01702

City

State Zip Code

Business License # / Type Class

Please check the trade or profession that this complaint pertains to:

Dental

Nursing

Pharmacy

___ Dentist

___ Licensed Practical Nurse

X Pharmacist

___ Dental Hygienist

___ Registered Nurse

___ Pharmacy Technician

X Drug Store

___ Warehouse Distributor

___ Nursing Home Administrator

___ Physicians Assistant

___ Perfusionist

___ Respiratory Care Therapist

Description of the Complaint:

Briefly describe the incidents that led to your complaint and note the times and dates that events occurred. List the names of all individuals involved. Please attach additional pages if needed.

Please see attached email that I
previously sent to your attention.

(Please use a separate sheet if necessary. Please do not write in the margins.)

Additional information or materials attached ☒ Yes ☐ No

To speed up processing your complaint, please submit legible copies (not the originals) of all relative documents supporting your complaint (i.e. contracts, medical records, cancelled checks, etc.). You will receive an acknowledgment letter with the name of the investigator assigned to your case.

AUTHORIZATION FOR RELEASE OF RECORDS AND REFERRAL OF COMPLAINT

My signature to this form, or a photocopy thereof, authorizes the Department of Public Health to:
(1) receive copies of all medical, dental and mental health records relating to my complaint, and (2) to refer my complaint to other appropriate law enforcement authorities to investigate and/or prosecute my complaint.

Please note that all complaints are investigated to determine their factual basis. The act of filing a complaint does not assure or imply that disciplinary action will be taken against the licensee.

I attest that the information provided is true, correct and complete to the best of my knowledge.


Complainant signature

4/27/04
Date

Mail this form to:
Department of Public Health
Division of Health Professions Licensure
239 Causeway St., Suite 400
Boston, MA 02114

Tuesday, April 27, 2004 11:53 AM
 'James.d.coffey@state.ma.us'
 New England Compounding Center Activity in the State of Wisconsin

To the Massachusetts Board of Pharmacy.

We today had contact with a Mr. [REDACTED] of the New England Compounding Center, Framingham, Ma. Due to the discussions that this individual had with one of my purchasing technicians and apparently, with personnel on our medical staff I am contacting you.

staff I am contacting you.

[redacted] is offering a product to our plastic surgery physician that he calls extra strength triple anesthetic cream that contains 20% Benzocaine, 6% Lidocaine, and 4% tetracaine. My first concern regards the safety of this product. I have been unable to locate literature to support the safety of these agents in combination and at these concentrations for topical use. And therefore his promotion of this product is, to me at least, problematic. My second concern is that [redacted] related to the purchasing technician that he would need a prescription for the product and that we could use the name of a staff member if we wanted to. He said "other institutions have used a nurses name." The technician then quered Mr. [redacted] as to the legality of the distribution method. He assured her that it was legal. He indicated that after we received the product it was up to us how we used it and to whom it was administered. It is my belief that this is unethical practice, is illegal and is in violation of the tenets of appropriate pharmacy compounding.

[redacted] choosing this methodology at this

I am more than willing to file a formal complaint if you believe one is warranted but am choosing this methodology at this time since I am not a resident of your state nor licensed to practice in your state.

I look forward to further communication.

Director of Pharmacy



DIVISION OF HEALTH PROFESSIONS LICENSURE

617-727-7406

Date Received (stamp):

Entered into the Database(Date):

Docket #:

Acknowledgement letter sent (Date):

Signature:

Please complete this form as fully as possible. (PLEASE DO NOT WRITE ABOVE LINE.) Please type or print legibly in ink
COMPLAINT BY:

Name:

Last Name

First Name

MI

Address:

Number

Street

City

State

Zip Code

Daytime Phone

Evening Phone

Best way to reach you: ☐ Evening Phone ☐ Daytime Phone ☐ E-mail:

COMPLAINT AGAINST (use separate form for each licensed individual):

Name:

Last Name

First Name

MI

Address:

Number

Street

City

State

Zip Code

Daytime Phone

License Number/Type Class

Business Name

Business Address

City

State

Zip Code

Business License #/Type Class

Please check the trade or profession that this complaint pertains to:

DentalNursingPharmacy

Dentist

Licensed Practical Nurse

Pharmacist

Dental Hygienist

Registered Nurse

Pharmacy Technician

☒ Drug Store

Warehouse Distributor

Nursing Home Administrator

Physicians Assistant

Perfusionist

Respiratory Care Therapist

Description of the Complaint:

Briefly describe the incidents that led to your complaint and note the times and dates that events occurred. List the names of all individuals involved. Please attach additional pages if needed.

11/23/04 Board voted for formal complaint
Dispensing medication w/o patient specific
prescriptions)

(Please use a separate sheet if necessary. Please do not write in the margins.)

Additional information or materials attached ☒ Yes ☐ No

To speed up processing your complaint, please submit legible copies (not the originals) of all relative documents supporting your complaint (i.e. contracts, medical records, cancelled checks, etc.). You will receive an acknowledgement letter with the name of the investigator assigned to your case.

AUTHORIZATION FOR RELEASE OF RECORDS AND REFERRAL OF COMPLAINT

My signature to this form, or a photocopy thereof, authorizes the Department of Public Health to:
(1) receive copies of all medical, dental and mental health records relating to my complaint, and (2) to refer my complaint to other appropriate law enforcement authorities to investigate and/or prosecute my complaint.

Please note that all complaints are investigated to determine their factual basis. The act of filing a complaint does not assure or imply that disciplinary action will be taken against the licensee.

I attest that the information provided is true, correct and complete to the best of my knowledge.

Complainant signature

Date

Mail this form to:

Department of Public Health
Division of Health Professions Licensure
239 Causeway St., Suite 400
Boston, MA 02114

November 23, 2004 Mass. Bd. Inspection Report
(Dockets DS-05-040/PH-05-066)

**MDPH-Division of Health Professions' Licensure****INVESTIGATION REPORT**

Page 1 of 7

Licensee Name: Barry Cadden

Docket No: DS 05-040

License Number: PH 21239

DS 2848

Priority Code: 2 Received by DHPL: 11/23/04 Docket Opened: 11/23/04

Assigned: 11/23/04

Investigator Name: James Emery- Health Care Investigator

Supervisor Name: Leslie Doyle - Program Coordinator

SECTION I: Demographics and History**A. LICENSEE INFORMATION:**

1. Name of Licensee/Respondent: Barry Cadden
2. Address of Record: [REDACTED]
3. Current Address: [REDACTED]
4. Phone Number(s): Home N/A Cell (N/A) Business (N/A) Fax (N/A)
Licensee/Respondent Date of Birth: [REDACTED]
5. License Type & No.: PH 21239 Current Status: C Exp. Date: 12/31/06
6. Original Date of Issuance: 10/9/90
7. Record of Standing Attached: Yes
8. Name of Educational Institution Attended: University of RI
Date of Graduation: 1990

B. OTHER MASSACHUSETTS LICENSES HELD: None

1. Profession/Trade:
2. License No. Current Status: Exp. Date: / /
3. Prior Discipline (explain): N
4. Certified Documentation Attached: ☐ Yes ☐ No

C. NON-MASSACHUSETTS LICENSES HELD: None

1. Profession / Trade:
2. License No. Current Status: Exp. Date: / /
3. Prior Discipline (explain):
4. Certified Documentation Attached: ☐ Yes ☐ No

D. LICENSEE'S EMPLOYMENT INFORMATION:

1. Current Employer: New England Compounding Center
2. Address: 697 Waverly St Framingham, MA 01702
3. Telephone Number: 508 820 0606

SECTION II: Interviews, Complainant Info & Index of Materials/Documents**A. INTERVIEWS CONDUCTED: List below and include labeled interview notes in case file.**

Individuals Interviewed (name/title)	When/Where? (dates/time of day)	Type Interview (In-person/phone)	Contact Information (phone, address, business)
1.			
2.			
3.			
4.			
5.			

MDPH-Division of Health Professions Licensure

INVESTIGATION REPORT

Page 2 of 7

Licensee Name: Barry Cadden
License Number: PH 21239

Docket No: DS 05-040
DS 2848

B. WITNESSES NOT AVAILABLE FOR INTERVIEW: Document attempts in case file

Individuals	Contact Information (phone, address, business)	Attempt(s) to contact (dates, times)
1.		
2.		
3.		

E. COMPLAINANT INFORMATION:

1. NAME OF COMPLAINANT: Board of Pharmacy
2. ADDRESS: 239 Causeway St, Boston, MA 02114
3. PHONE NO: (617) 727 0086 CELL PHONE: (N/A)

D. INDEX OF MATERIALS/DOCUMENTS: Label documents/materials as noted below in order of presentation in the file

ITEM 1: Complaint

ITEM 2: Record of Standing

ITEM 3: Staff assignment 05-006

ITEM 4: NECC Order Form

ITEM 5:

ITEM 6:

ITEM 7:

ITEM 8:

SECTION III: Investigation Summary

Allegation of Complaint: Failure to adhere to the standards of practice, specifically compounding and dispensing of a medication without a valid prescription (non patient specific)

Describe documentation/facts that support allegations:

Staff assignment presented at Board meeting of 11/23/04. Board voted to bring staff assignment to formal complaint.

Describe documentation/facts that do not support allegations: None

TYPE OF ERROR:

- ☐ WRONG STRENGTH
- ☐ WRONG DRUG
- ☐ WRONG DIRECTIONS
- ☐ WRONG PATIENT
- ☐ OTHER - blisterpak information was incorrect
- ☐ DRUG / DIRECTIONS DOSE PRESCRIBED
- ☐ DRUG / DIRECTIONS DOSE DISPENSED
- ☐ DISPENSED RX LABEL CORRECT
- ☐ DISPENSED LABEL INCORRECT
- ☐ NEW PRESCRIPTION
- ☐ REFILL PRESCRIPTION
- ☐ INGESTION OCCURRED

MDPH-Division of Health Professions Licensure

INVESTIGATION REPORT

Page 3 of 7

Licensee Name: Barry Cadden

Docket No: DS 05-040

License Number: PH 21239

DS 2848

☒ OTHER- Failure to adhere to the standards of practice, specifically compounding and dispensing of a medication without a valid prescription (non patient specific)

***Board should review item #4. NECC Order Form provided in response. Form is non-compliant by Board determination. NECC was notified by telephone (Greg Conigliaro) that the form currently used is non-compliant and must stop the use of this form immediately.

PATIENT STATUS:

A. Setting Where Alleged Incident/Conduct Occurred:

1. Current Employer: New England Compounding Center

2. Address: 697 Waverly St Framingham, MA 01702

3. Telephone Number: 508 820 0606

Contact and Title: Barry Cadden, Manager of Record

1. If employed by another entity other than where the alleged incident occurred:

Name: N/A

Address N/A

Phone No: N/A

Contact Person: N/A

Contact's Title: N/A

Licensee's Supervisor (if applicable give name): N/A

Phone number

B. Attorney of Record:

NA

1. Name of Attorney:

2. Name of Firm:

3. Address:

4. Phone No(s).

Fax No. ()

D. Investigator's Activities and Findings:

Describe - who, what, where, when, and why.

1. Complainant's allegation: Failure to adhere to the standards of practice, specifically compounding and dispensing of a medication without a valid prescription (non patient specific)

2. Licensee's response: A review of the same documentation provided to you does show what would appear to be incorrect or repetitive names being provided by several of our prescribing physicians. We have instituted a new Standard Operating Procedure for the Quality Check and Vetting of Patient Names, which should eliminate these inconsistencies in the future. This new SOP is included herein at "Attachment A." Additionally, per Leslie Doyle's last inspection, the newest version of the Prescription Order Form, included herein as "Attachment B," specifically includes a Verification Step

MDPH-Division of Health Professions Licensure

INVESTIGATION REPORT

Page 4 of 7

Licensee Name: Barry Cadden

Docket No: DS 05-040

License Number: PH 21239

DS 2848

at the bottom which requires a Registered Pharmacist or designee, to verify all items shown on the Patient Order Form, including patient names.

Summary of events from medical records:

4. Describe any information learned or submitted that does not support the Allegation: None

5. Describe any information requested and not received: None

6. Other Information: N/A

Patient Record:

Charting: ☐ Perio

☐ Hard Tissue

☐ Soft Tissue

☐ Medical History

☐ Treatment Plan

☐ Informed Consent

☐ Radiographs

☐ Anesthesia Record

☐ CPR Certification

☐ On-Site Inspection (optional)

7. Describe any exhibits not in case file (study models, radiographs, tapes, etc.). Describe location and with whom.

NA

8. List other state/federal or municipal agencies involved or also investigating this case and include contact information (name, address, telephone no.)

E. COMPLAINT HISTORY

1. Companion Complaints: (list docket numbers, allegations, status, and disposition)

2. Complaint Pending Board: None

3. Complaints Pending Prosecutions: None

4. Related Complaints: (list docket numbers, allegations, status, and disposition) None

5. Prior Complaints: (list docket numbers, allegations, status, and disposition)

20021211DS036- Unprofessional conduct-Dismissed, advisory letter

20030212DS055- Failure to adhere to the standards of practice-PB

20030226DS060- Failure to adhere to the standards of practice, Dismissed, Advisory letter

20040504DS062- Unethical conduct- Dismissed, Advisory letter

19990330PH066- Unprofessional Conduct-Dismissed, informal reprimand

20021211PH042- Unprofessional Conduct-Dismissed, Advisory letter

20030212PH066- Failure to adhere to the standards of practice-PB

20030226PH070- Failure to adhere to the standards of practice-Dismissed, Advisory letter

MDPH-Division of Health Professions Licensure

INVESTIGATION REPORT

Page 5 of 7

Licensee Name: Barry Cadden

Docket No: DS 05-040

License Number: PH 21239

DS 2848

6. Criminal Offender Records Information Check (CORI) been performed? Yes

Include certified copies of judgments: No

F. In your opinion should case go to Medical Error Triage: No

Explain:

G. Summary of alleged violation(s) of regulation/statutes (Include description of licensee's actions that constitute the basis of the violation(s).)

H. Staff Recommendation(s):

☐ Dismissal with Prejudice:
No Violation

☐ Probation
☐ Terms:

☐ Dismissal without Prejudice
☐ Lack of Sufficient Evidence

☐ Censure

X Dismissal with Advisory Letter

☐ Offer Voluntary Surrender
☐ Terms:

☐ Stayed Probation
☐ Terms:

☐ Summary Suspension
☐ Terms:

☐ Reprimand

☐ Revocation
☐ Terms:

CONTINUING EDUCATION REQUIREMENTS:

Enclosed

OTHER TERMS: MPRS evaluation

INVESTIGATOR SIGNATURE: _____

DATE: _____

SUPERVISOR SIGNATURE: _____

DATE: _____

Complaint Committee Decision/Recommendation: CC Meeting Date:

Re: Staff recommendation:

☐ CC Agrees ☐ CC Disagrees (making the following recommendation)

☐ Dismissal with Prejudice:
☐ No Violation

☐ Probation
☐ Terms:

☐ Dismissal without Prejudice
☐ Lack of Sufficient Evidence
☐ Dismissal with Advisory Letter

☐ Censure
☐ Offer Voluntary Surrender
☐ Terms:

☐ Stayed Probation
☐ Terms:

☐ Summary Suspension
☐ Terms:

MDPH-Division of Health Professions Licensure

INVESTIGATION REPORT

Page 6 of 7

Licensee Name: Barry Cadden

Docket No: DS 05-040

License Number: PH 21239

DS 2848

☐ Reprimand

☐ Revocation

☐ Terms:

CONTINUING EDUCATION REQUIREMENTS:

OTHER TERMS:

Summary of alleged violation(s) of regulation/statutes (include description of licensee's actions that constitute the basis of the violation(s)):

Notes:

BOARD'S Decision/Recommendation: Board Meeting Date:

Re: Staff or/ CC recommendation:

☐ Board Agrees ☐ Board Disagrees (making the following recommendation)

☐ Dismissal with Prejudice:

☐ Probation

☐ No Violation

☐ Terms:

☐ Dismissal without prejudice

☐ Censure

☐ Lack of Sufficient Evidence

☐ Offer Voluntary Surrender

☐ Dismissal with Advisory Letter

☐ Terms:

☐ Stayed Probation

☐ Summary Suspension

☐ Terms:

☐ Terms:

☐ Reprimand

☐ Revocation

☐ Terms:

CONTINUING EDUCATION REQUIREMENTS:

OTHER TERMS:

Summary of alleged violation(s) of regulation/statutes (include description of licensee's actions that form the basis of the violation(s)):

Notes:

Votes:

MDPH-Division of Health Professions Licensure

INVESTIGATION REPORT

Page 7 of 7

Licensee Name: Barry Cadden
License Number: PH 21239

Docket No: DS 05-040
DS 2848

DISPOSITION OF CASE:

Refer to Board Counsel / Date:

Refer to Prosecution / Date:

Other

BOARD OF REGISTRATION IN PHARMACY File Review

Summary of Outstanding complaints

Allegation.

Licensee response:

Licensee:

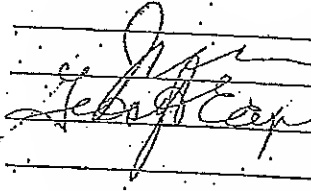
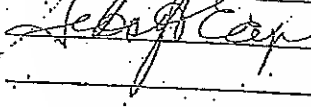
Recommended action (choose one):

- 1) STAFF ASSIGNMENT BRNG TO COMPLAINT: ☒
3) ADVISORY LETTER ☒
5) NO VIOLATION - DISMISS ☐
7) LACK OF JURISDICTION - DISMISS ☐
9) ADDITIONAL CEU'S - DISMISS ☐
11) Licensee is offered to enter MPRS: ☐

- 2) INFORMAL CONFERENCE ☐
4) DISMISS ☐
6) LACK OF EVIDENCE - DISMISS ☐
8) DISMISS - without prejudice ☐
10) INVESTIGATOR - FOLLOW-UP ☐

Board of Registration in Pharmacy- Reviewed by: (two signatures required)

James Devita - RPH President:
Karen Ryle - RPH Secretary:
Harold Sparr - RPH Member:
Dr. Donald Accetta: Member
Joel Berman - RPH Member:
George Cayer - RPH Member:
William Gouveia RPH Member:
Sophia Pasedis RPH Member:
Marilyn Barron: Public Member
Steve Budish Public Member

_____	DATE _____
_____	DATE _____
_____	DATE _____
_____	DATE _____
	DATE 11/23/04
	DATE 11/23/04
_____	DATE _____
_____	DATE _____
_____	DATE _____
_____	DATE _____

*July 27, 2012 Email Forwarding CO Complaint to
Mass. Bd. Counsel*

Senatore, Joan (EHS)

From: Coffey, James D (DPH)
Sent: Friday, July 27, 2012 7:34 AM
To: Manning, Susan (DPH); [REDACTED] (DPH); [REDACTED] (DPH); [REDACTED] (DPH); [REDACTED] (DPH); [REDACTED] (DPH)
Subject: FW: New England Compounding Center
Attachments: NECC.pdf
FYI for follow up discussion

JD

From: Coffey, James D (DPH)
Sent: Friday, July 27, 2012 7:33 AM
To: 'Manning, Susan'
Subject: RE: New England Compounding Center

[REDACTED]

Please be advised that I am in receipt of the special report.

The Massachusetts Board of Pharmacy will respond as soon as possible following a thorough review and analysis of the same.

If additional information is necessary, please contact me at 617 973 0950.

Sincerely, JD

James D. Coffey
Director
Massachusetts Board of Registration in Pharmacy
Department of Public Health
Division of Health Professions Licensure
239 Causeway Street, Suite 500, 5th Floor
Boston, MA 02114

[REDACTED]
Telephone (617-624-2000)
Facsimile (617-624-2000)
Website: <http://www.mass.gov/dph/boards/pharmacy>

From: Manning, Susan [mailto:Susan.Manning@state.ma.us]
Sent: Thursday, July 26, 2012 3:06 PM
To: Coffey, James D (DPH)
Subject: New England Compounding Center

James

Attached is the Special Report submitted to the Chief Inspector for the Pharmacy Board in Colorado concerning the receipt of non-patient specific compounded products into Colorado. Included in this

11/3/2012

report is the email correspondence with Regina Barrell with the FDA. Her direct phone number is ~~303.233.3333~~, and her email is ~~regina.barrell@fda.gov~~.

I would appreciate any information that the Massachusetts Board could provide concerning if this practice is allowed under Massachusetts pharmacy law.

Thank you.

~~See~~

~~See~~

**Pharmacy Inspector
Colorado Department of
Regulatory Agencies**

Division of Registrations

Board of Pharmacy

1560 Broadway, Suite ~~1560~~

Denver, CO 80202

P ~~303.233.3333~~ | F ~~303.233.3333~~

www.dora.state.co.us



CONFIDENTIALITY NOTICE: This message is intended only for the use of the individual to whom it is addressed and may contain information that is privileged, confidential and exempt from disclosure under applicable law. If you are not an intended recipient you are not authorized to disseminate, distribute or copy this e-mail. Please notify the sender immediately if you have received this e-mail by mistake and delete this e-mail and any attachments from your system.

July 20, 2012 Complaint Against NECC from Colorado

THE COLORADO STATE BOARD OF PHARMACY
Special Report

Date: 20 July 2012

Inspector: Susan S. Martin

Subject: New England Compounding Pharmacy, Inc. (WHO 7832)

Background:

On 7/17/12, I visited Delta County Memorial Hospital, 1501 E. 3rd St. Delta, CO 81416 to conduct a routine inspection. While reviewing the records of receipt for prescription drugs, I located an invoice from New England Compounding Center, Inc., PO Box 4146, Woburn, MA 01888-4146 detailing receipt of a quantity of 46 hyaluronidase 150U/ml, 1 ml Injection (a compounded prescription drug) on 6/28/12 (Attachment 1). I asked the pharmacist manager, Mark Carlton (RPH 11282), if they had any of this product in the pharmacy. He showed me a container of vials of this product and I took several pictures of one (Attachment 2). Upon return to the office, I searched the CAVU E-License database (the licensing database for the Colorado Department of Regulatory Agencies) for information concerning New England Compounding Center Inc.'s registration status. The name "New England Compounding Center, Inc." is not found in the E-License database, however, the following entities were located (Attachment 3):

- 1) New England Compounding Center is the DBA (doing business as) and owner of New England Compounding Pharmacy, Inc., an out-of-state wholesaler located at 697 Waverly St., Framlingham, MA 01702 (WHO 7832).
- 2) New England Compounding Center is an out-of-state pharmacy, located at 697 Waverly St., Framlingham, MA 01702 (OSP 5402).

Neither of these registered entities is located at the address on the Invoice from New England Compounding Center, Inc.

On 7/16/12, I spoke with Regina Barrell from the Food and Drug Administration to inquire whether New England Compounding Center, Inc. was registered as a manufacturer. She confirmed that they were not (Attachment 4).

During a routine inspection in 2011, Inspector Lisa Cornett located documentation of unregistered/unlicensed distribution of prescription drugs into Colorado by New England Compounding Center, Inc. (Attachment 5). As a result of her investigation, Case 2011-3973 was initiated and a Cease and Desist Order was issued to New England Compounding Center, Inc. on 4/15/11 (Attachment 6).

Attachment 1



New England Compounding Center, Inc.
 PO Box 4146
 Woburn, MA 01888-4146
 Ph. 508-820-0606
 Fx. 508-820-1616

Invoice

Date	Invoice #
6/28/2012	220566

Bill To
DELTA COUNTY MEMORIAL HOSPITAL 1501 EAST 3RD STREET DELTA, CO 81416 ATTN: BONNIE MILLER/PHARMACY

Ship To
DELTA COUNTY MEMORIAL HOSPITAL 1501 EAST 3RD STREET DELTA, CO 81416 ATTN: INPATIENT PHARMACY

P.O. Number	Terms	Rep	Ship	Via	F.O.B.	Account#
	Net 30	MD-H	6/28/2012	FEDEX		
Quantity	Item Code	Description			Price Each	Amount
46	HY150/1	HYALURONIDASE 150U/ML, 1ML INJ.			18.00	828.00
1	Shipping Charges				20.00	20.00
!!!THANK YOU FOR YOUR ORDER!!!					Total	\$848.00
* PLEASE PLACE INVOICE NUMBER ON PAYMENT *						

Attachment 2

HYALURONIDASE

lot# 061120120

MDV **REFRIG

1ML

SMALL INJECTION

12/18/2001



Attachment 3

Credential View Screen [update]

New England Compounding Pharmacy, Inc. DBA: New England Compounding Center Address: <input checked="" type="radio"/> Public <input type="radio"/> Mail <div style="border: 1px solid black; padding: 2px;"> [change public address] New England Compounding Pharmacy, Inc. 697 Waverly St Framingham, MA 017020000 </div>	ID: 809876 Warnings: SSN/FEIN: 04-3407495 Missing SSN/FEIN Reason: Contact Standing: Active Contact Type: BUSINESS Public File: YES Mailing List: US Citizen: Email: licensing@necorx.com	Contact Audit Enforcement Cont. Edu Documents Owners Owned By/k Exams Experience Notes Schools Application Other State Background Online Info
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Comments:

Wholesaler Out-of-State [update] [form letter]

Credential #: WHO.0007832 Application Date: 06/06/2011 Effective Date: 08/24/2011 Expiration Date: 10/31/2012 First Issuance Date: 08/24/2011	Credential Status: Active (08/24/2011) Status Reason: CURRENT Approved By: LEGACYDATA, DORA Amount Due: \$0.00 Date Last Activity: Last Updated by: Certificate Sent Date: Work Queue: EEGLASSER, DORA	Audit Documents Verification Workflow Key Mgmt Fees Notes Print Docs Comp. Audit Renewal Legacy License Stat Online Infort
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Comments:

- Exemption
- User Defined License Data
- Workflow
- Legacy

Exemption [show all] [add]

Description	Active	Inactive
No active classifications.		

- [View Application Checklist](#)
- [View Communication Log](#)
- [View Deposit Information](#)
- [View License Fees History](#)
- [View License History](#)

Credential View Screen [update]



New England Compounding Center Address: <input checked="" type="radio"/> Public <input type="radio"/> Mail <div style="border: 1px solid black; padding: 2px; margin-top: 5px;"> [change public address] New England Compounding Center 697 WAVERLY ST FRAMINGHAM, MA 01702 </div>		ID 828223 Warnings SSN/FEIN Missing SSN/FEIN Reason Contact Standing Active Contact Type BUSINESS Public File YES Mailing List US Citizen Email: licensng@neccrx.com	Contact Audit Enforcement Cont. Edu Documents Owners Owned By/k Exams Experience Notes Schools Application Other State Background Online Info:
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Comments:

Prescription Drug Outlet-Out-of-State [update] [form letter]

Credential # OSP.0005402 Application Date Effective Date 11/01/2010 Expiration Date 10/31/2012 First Issuance Date 02/24/2003	Supervision Warnings Type License Inoperable Credential Status Active (11/01/2010) Status Reason CURRENT Approved By LEGACYDATA, DORA Amount Due \$0.00 Date Last Activity Last Updated by Certificate Sent Date	Audit Documents Verification Workflow Key Mgmt Fees Notes Print Docs Comp. Audit Renewal Legacy License Stat Online Infor
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Comments:

- Supervised By
- User Defined License Data
- Workflow
- Legacy

User Definable License Data

Field	Value
OSP - License Method	Original
DEA Number	BN5927819

[update]

Field	Value
-------	-------

- [View Communication Log](#)
- [View License Fees History](#)
- [View License History](#)
- [View Renewal Attachment](#)
- [View Renewal Entry Checklist](#)

Attachment 4

Martin, Susan

From: Barrell, Regina A <Regina.Barrell@fda.hhs.gov>
Sent: Monday, July 16, 2012 2:54 PM
To: [REDACTED]
Cc: Wardwell, Amber; Ota, Bruce R; Archdeacon, Karen N
Subject: FW: New England Compounding Center (NECC)
Attachments: Attachment - 1.pdf; Attachment - 2.pdf; Attachment - 3.pdf; hppscan45.pdf

Hi [REDACTED]:

I checked our Registration database and New England Compounding Center is not listed as having registered with us as a manufacturer. With this e-mail, I am copying our New England District Compliance staff with the information you provided (invoice for the Injectable hyaluronidase to Delta County Memorial Hospital) along with the Cease and Desist documents [REDACTED] sent last year regarding NECC (see e-mail string below). I would suggest you get in touch with the Massachusetts Board of Pharmacy if you haven't already to inform them of the firm's activity and to see if there are any actions they may wish to take especially in light of your Cease and Desist Order.

I also checked the status of Wedgewood Pharmacy in New Jersey. They also are not listed in our database as having registered as a manufacturer. Under a separate e-mail, I will copy our New Jersey District Office with the invoice you collected, but as in the NECC case, you may wish to contact your counterparts with the New Jersey Board of Pharmacy.

Let me know if you have any questions or wish to discuss further.

Regina

From: Wardwell, Amber
Sent: Tuesday, May 10, 2011 3:07 PM
To: Barrell, Regina A; Archdeacon, Karen N; Ota, Bruce R
Subject: FW: New England Compounding Center (NECC)

Thanks [REDACTED],

Bruce Ota is the CO for NECC. I'll ask him to follow up if we have any questions.

[REDACTED]

From: Barrell, Regina A
Sent: Tuesday, May 10, 2011 4:19 PM
To: Wardwell, Amber; Archdeacon, Karen N
Subject: FW: New England Compounding Center (NECC)

Hi [REDACTED] and [REDACTED]:

I had a phone call with [REDACTED] of the Colorado Board of Pharmacy regarding New England Compounding Center (NECC). Attached is the background information from [REDACTED] as well as the Cease and Desist Order that the Board issued to NECC regarding their illegal distribution of compounded drugs to hospitals in the Denver metropolitan area. The firm is neither registered or listed with the State to do business as a drug outlet. I know that you have some previous reg history with this firm and that they were the recipient of at least one warning letter. This is just FYI but if you have any questions, please feel to give me a call to discuss.

From: ~~Chris [mailto:Chris@Colorado.gov]~~

Sent: Tuesday, May 10, 2011 12:29 PM

To: ~~Bernell, Regina~~

Subject: New England Compounding Center (NECC)

Hi ~~Bernell~~,

Attachment – 1 is the report and exhibits that lead to the Cease and Desist Order;

Attachment – 2 is additional documents Pharmacy Board staff obtained at another facility (while related to NECC, it's unrelated to what actually led to the Cease and Desist Order); and

Attachment – 3 is the actual Cease and Desist Order.

As always, thanks for your help.

~~Chris~~

Chief Pharmacy Inspector

Colorado Department of

Regulatory Agencies

Division of Registrations

Board of Pharmacy

1560 Broadway, Suite ~~1500~~

Denver, CO 80202

P ~~303.733.7227~~ | F ~~303.733.1777~~



CONFIDENTIALITY NOTICE: This message is intended only for the use of the individual to whom it is addressed and may contain information that is privileged, confidential and exempt from disclosure under applicable law. If you are not an intended recipient you are not authorized to disseminate, distribute or copy this e-mail. Please notify the sender immediately if you have received this e-mail by mistake and delete this e-mail and any attachments from your system.

Attachment 5

THE COLORADO STATE BOARD OF PHARMACY
Special Report

Date: 13 April 2011

Inspector: Lisa A. Cornett

Subject: New England Compounding Center, Inc., OSP 5402

Issue: Unregistered/Unlicensed Distribution of Prescription Drugs Into Colorado

Details:

On 04/5/11, I conducted a routine inspection of Sky Ridge Medical Center, (PDO 168-01), 10101 Ridgeway Pkwy, Lone Tree, CO 80124. During the inspection, I collected records detailing the receipt of prescription drugs purchased from New England Compounding Center, Inc., PO Box 4146, Woburn, MA, 01888, a non-resident prescription drug outlet. This is a violation of CRS 12-22-130(2) and CRS 12-22-802(1).

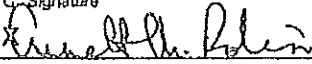
Attachment 6

CERTIFICATE OF SERVICE

This is to certify that I have duly served the within CEASE AND DESIST ORDER upon all parties herein by depositing copies of same in the United States mail, first-class postage prepaid, at Denver, Colorado, this 15th day of April, 2011, addressed as follows:

New England Compounding Center, Inc.
Attn: Designated Representative
697 Waverly St
Framington, MA 01702



SENDER: COMPLETE THIS SECTION		COMPLETE THIS SECTION IF DELIVERY	
<input type="checkbox"/> Complete Items 1, 2, 3. Also complete Item 4 if Restricted Delivery is desired. <input type="checkbox"/> Print your name and address on the reverse so that we can return the card to you. <input type="checkbox"/> Attach this card to the back of the mailpiece, or on the front if space permits.		A. Received by (Please Print Name) _____ B. Date of Delivery _____	
1. Article Addressed to: <div style="border: 1px solid black; padding: 5px; margin: 10px 0;"> New England Compounding Center Attn: Designated Representative 697 Waverly St Framington, MA 01702 </div>		C. Signature  <input type="checkbox"/> Agent <input type="checkbox"/> Addressee	
		D. Is delivery address different from Item 1? <input type="checkbox"/> Yes If YES, enter delivery address below: <input type="checkbox"/> No <div style="text-align: center; margin-top: 10px;"> JUL 20 2009 </div>	
		3. Service Type <input checked="" type="checkbox"/> Certified Mail <input type="checkbox"/> Express Mail <input type="checkbox"/> Registered <input type="checkbox"/> Return Receipt for Merchandise <input type="checkbox"/> Insured Mail <input type="checkbox"/> C.O.D.	
		4. Restricted Delivery? (Extra Fee) <input type="checkbox"/> Yes	
2. Article Number (Copy from service label)		7001 0360 0001 5987 0247	

January 26, 2005 – FDA Memo Re

Sep 24, 2004 NECC Inspection



14-50 10000000

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

NEW ENGLAND DISTRICT
MEMORANDUM

Date January 26, 2005

From Paraluman S. Leonin, CSO
NWE-DO

Subject Inspection/Investigation of
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

To Kathleen Anderson, Acting Team Leader
Compounding Team, HFD-316
Division of New Drugs & Labeling Compliance

Thru Ellen P. Madigan, SCSO ✓
NWE-DO

An investigation/limited inspection of this Compounding Pharmacy was conducted jointly with the Massachusetts Board of Pharmacy (MABP) per request of CDER, Division of New Drugs & Labeling Compliance, Compounding Team, HFD-316 (FACTS 536354). This investigation was mainly to obtain information about the firm's compounding practices, as they relate to the compounding of Trypan blue products.

I was accompanied on this investigation/limited inspection of the New England Compounding Center (NECC) by Mr. James Emery, Investigator & Mr. Leo McKenna III, Quality Assurance Coordinator, who are both from the MABP.

On September 23, 2004 our credentials were shown & FDA 482, Notice of Inspection, was issued to Mr. Barry Cadden, Director of Pharmacy & Owner of the New England Compounding Center (NECC). Mr. Cadden acknowledged that he is the most responsible person in the firm. I was introduced to Mr. Gregory A. Conigliaro, General Manager & Co-Owner of NECC. Mr. Conigliaro reported that he just joined the company about eight months ago & that he is a Civil Engineer by profession. He provided the following information. The corporate structure of NECC is as follows:

President	-	Carla Conigliaro
Vice President	-	Barry Cadden
Treasurer	-	Greg Conigliaro
Clerk	-	Sheri Han

I asked Mr. Cadden if the corrective actions that were promised by him on the last EI of 2/10/03 were already implemented. Last EI of 2/10/03 was classified "OAI" with referral to Massachusetts State Board of Pharmacy. FDA 483, Inspectional Observations, was issued for: (1) inadequate documentation to verify sterile drug products dispensed meet set of standards, such as specifications or assigned shelf life; (2) no SOPS for handling complaints and failure to maintain complaint files; and (3) lack of documentation for a specific reported adverse event.

Inspection of firm's new set of procedures & related documents showed that corrective actions have been implemented.

I asked Mr. Cadden if he is compounding & dispensing Trypan Blue. He said he does. I asked him if he has anything in stock. He said no, because he just compounds the drug if he receives the prescriptions for certain patients. While showing us the "Clean Room" where compounding takes place, we had to pass through a small laboratory where some tests were being performed. I noticed a drawer that was identified as "Trypan Blue". I requested him to open the drawer. There were 189-1ml vials of Trypan Blue PF 0.1% Injectable; Lot #07272004. See labeling shown as Exhibit #1. I told Mr. Cadden that Trypan Blue is not an FDA approved product & as such he should not be compounding & dispensing it. Mr. Cadden stated that he did not know that it is not an approved product. He told one of the employees in the laboratory to put the vials in quarantine which he told us will be eventually destroyed.

I told Mr. Cadden that I have to obtain some information from him as part of my assignment.

I gave Mr. Conigliaro a list of some of the questions in the assignment (#3, 4, 5, 7, 10, 11, 12, 15, 16 & 17). I did not list down the other questions in the assignment because I thought that it would be better if I ask him the questions directly.

Mr. Cadden stated that he will have to talk with his lawyer if it is okay to supply the information/answer the questions I had given him. He also stated that his lawyer is on vacation & would not be back until 9/27/04. The lawyer's name is Jonathan Tamkin from Newton, MA.

Mr. Emery, Mr. McKenna & I went back to the firm on 9/28/04 & met with Mr. Cadden & Mr. Conigliaro.

I asked Mr. Conigliaro if he was able to answer the questions I had listed down on our last visit. He stated that he has made some responses to the questions/information I had requested, in draft form & that he has to show their lawyer for approval before he could give it to me.

I requested Mr. Cadden for Trypan Blue labels which he provided (see Exhibit #2). A copy of the Certificate of Analysis for Trypan Blue (Exhibit #3) that came with the shipment of the Trypan Blue raw material that was in stock, Lot #C107217, was obtained. The supplier was PCCA, Houston, Texas.

The following information was obtained from Mr. Cadden when I questioned him about the one hundred eight nine (189) vials of Trypan Blue that I found in one of the drawers in the laboratory that was labeled "TYRPAN BLUE" on 9/23/04.

- He did not have to put the Trypan Blue vials in quarantine, which would eventually be destroyed as he told me on 9/23/04, after they had spoken to their lawyer.
- Their lawyer had told them that there is no regulation which states that Compounding Pharmacies cannot compound FDA non-approved drugs.
- That he dispensed Trypan Blue on 9/24, 25, 26, 27 & 28/04 as shown in log (Exhibit #4).
- That he intends to compound & dispense Trypan Blue until FDA/MABP will put in writing that they cannot compound it & dispense it and the reason why.

When I started asking Mr. Conigliaro the rest of the questions in the assignment, he became indignant & he said that he does not really have the time to sit with us & answer all those questions. He said if I could give him the list of questions, he would prepare the answers & give everything to me in one piece, after he shows it to their lawyer.

Mr. Cadden also told Mr. Conigliaro, "Don't answer anymore questions!"

Mr. Conigliaro questioned how Trypan Blue came into the picture. I told him it is part of my assignment from headquarters. Then he wanted to know specifically who issued the assignment & I gave him Kathy Anderson's name. He also started questioning FDA's jurisdiction on Compounding Pharmacies.

I told Mr. Conigliaro that FDA received a complaint re: Trypan Blue, so we have to do our investigation, because FDA has to respond to the complaint & we have to notify MABP also.

Mr. Conigliaro asked me who the complainant was & I told him I don't know. He said it's probably one of their competitors. He also said that he was sorry if he sounded mean. He explained that he had to leave early, had a lot of things to finish & just did not have the time to sit with us to answer our questions.

I wrote down the remaining list of questions in the assignment & left them with Mr. Conigliaro.

On October 1, 2004, I received a 22-page fax document from Mr. Conigliaro, which constituted his responses to the written questions I had given him. This was followed by a hardcopy (Exhibit #5) which I received on October 5, 2004. I showed these responses to Ms. Ellen Madigan, SCSO & Ms. Ann Simoneau, CO, NWE-DO to update them about the status of the assignment & told them about the firm's attitude.

I requested Mr. Emery for a copy of a written report of what sanctions were taken by the MABP as follow-up from the EI of 2/03. Mr. Emery stated that the cases are still pending Board & as such are not releasable at that time. The assignment in regards to Trypan Blue is also pending Board & when they become releasable, he will forward them to me.

I told Mr. Emery that I am scheduled for a foreign inspection & will not be back until the fourth week of November 2004. In addition, I told Mr. Emery that I will not be available to go back to the firm until after the holidays are over because I have to write three reports for my foreign inspection. This situation & the firm's attitude were also relayed to Kathy Anderson.

On January 3, 2005, I received a copy of a letter, dated October 27, 2004 (Exhibit #6) sent by Mr. Emery from MABP to Mr. Barry Cadden. I also received a copy of Mr. Cadden's response letter to Mr. Emery, dated November 8, 2004 (Exhibit #7) stating the corrective actions to be undertaken/undertaken by NECC. I showed these letters to SCSO Ellen Madigan & CO Ann Simoneau & my plan to close out the inspection.

Mr. Emery was able to obtain a log of Trypan Blue that was compounded & dispensed from January 12, 2004 to September 28, 2004 (Exhibit #8), with some prescriptions attached. These prescriptions are examples of patients in the log who were dispensed at least more than one or two vials of Trypan Blue.

On January 18, 2005, I notified Mr. Emery that we do not have to go back to NECC to close out the inspection & that I'm doing it over the phone.

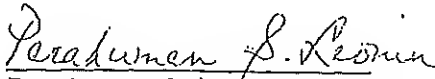
On January 19, 2005, I telephoned Mr. Barry Cadden & informed him that we are closing out the inspection based on his response letter to Mr. Emery of the MABP, indicating his plan of corrective actions, which will also be forwarded to headquarters. Before our conversation ended, Mr. Cadden asked me, "Do you think headquarters knew that Trypan Blue would be approved before the assignment was issued?" I said I really don't know. Our conversation ended at this point & the inspection was ended.

ATTACHMENT:

Assignment from Compounding Team Leader, HFD-316
FDA-482, Notice of Inspection

EXHIBITS:

- #1. Label of Trypan Blue PF 0.1% Injectable 1 ML vial
- #2. Labeling of Trypan Blue used for shipment
- #3. Certificate of Analysis for Trypan Blue LOT #C107217 from PCC
- #4. Log of Trypan Blue Compounded & Dispensed (9/24-28/04)
- #5. Responses to questions on assignment sent by Mr. Conigliaro, dated October 1, 2004
- #6. Letter sent by Mr. James Emery from MABP to Mr. Barry Cadden, dated October 27, 2004
- #7. Response letter sent by Mr. Barry Cadden, dated November 8, 2004, to Mr. James Emery, MABP
- #8. Log of Trypan Blue compounded & dispensed from January 12 – September 28, 2004


Paraluman S. Leonin, CSO
NWE-DO

cc: Ann Simoneau, Compliance Officer
NWE-DO

December 4, 2006 – Warning Letter From FDA to NECC



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

W.L-File

One Montvale Avenue
Stoneham, Massachusetts 02180
(781) 596-7700
FAX: (781) 596-7896

WARNING LETTER
NWE-06-07W

VIA FEDERAL EXPRESS

December 4, 2006

Barry J. Cadden, Director of Pharmacy and Owner
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

Dear Mr. Cadden:

On September 23, 2004, investigators from the U.S. Food and Drug Administration (FDA) and the Massachusetts Board of Pharmacy inspected your firm, located at 697 Waverly Street, Framingham, Massachusetts. On January 19, 2005, the inspection was completed. This inspection revealed that your firm compounds human prescription drugs in various dosage forms and strengths.

We acknowledge the receipt of your October 1, 2004, letter addressed to FDA's New England District Office, concerning questions presented during the referenced inspection.

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective," is supported by substantial judicial authority. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); *Prof'ls & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); *In the Matter of Establishment Inspection of Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd*, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

The drugs that pharmacists compound are not FDA-approved, and lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a

physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see *Notice of Availability*, 67 Fed. Reg. 39,409 (June 7, 2002)).¹ The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds finished drugs from bulk active ingredients that are not components of FDA-approved drugs, without an FDA sanctioned investigational new drug application (IND). The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Copies of Commercially Available Drug Products:

It has come to our attention that you are compounding trypan blue ophthalmic products. During the inspection at your firm, you advised an investigator from FDA's New England District Office that the trypan blue products that your firm compounds are devices. FDA classifies trypan blue products as drugs, not devices. Further, on December 16, 2004, trypan blue ophthalmic solution was approved by FDA and it is commercially available. As stated in the CPG, FDA will not exercise its enforcement discretion for the compounding of copies of commercially available FDA-approved products, including this one.

We have also learned that your firm may be compounding 20% aminolevulinic acid solution (ALA). Please note that there is a commercially available, FDA-approved aminolevulinic acid solution 20%. Like compounded trypan blue, FDA regards compounded 20% aminolevulinic acid solution as a copy of commercially available drug.

¹ Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court's ruling in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech. And those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002); the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

FDA does not sanction the compounding of copies of FDA-approved, commercially available drugs and the agency will not exercise its enforcement discretion regarding the trypan blue and ALA products compounded by your firm.

All products compounded by your firm containing trypan blue or ALA are drugs within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). These products are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. They are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA and they lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

2. Anesthetic Drug Products:

Equally serious, your firm's promotional materials reveal that it offers to compound "Extra Strength Triple Anesthetic Cream" which contains 20% benzocaine, 6% lidocaine, and 4% tetracaine. Like a manufacturer, you have developed a standardized anesthetic drug product that you sell under the name "Extra Strength Triple Anesthetic cream." Further, you generate sales by giving physicians "courtesy prescriptions" (i.e., free samples). These actions are not consistent with the traditional practice of pharmacy compounding, in which pharmacists extemporaneously compound reasonable quantities of drugs upon receipt of valid prescriptions from licensed practitioners to meet the unique medical needs of individual patients.

Moreover, the agency is concerned with the public health risks associated with the compounding of "Extra Strength Triple Anesthetic Cream." There have been at least two non-fatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high doses of local anesthetics. Local anesthetics, like "Extra Strength Triple Anesthetic Cream," may be toxic at high dosages, and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic, i.e. they have low therapeutic index.

Adverse events consistent with high systemic exposures to these products include seizures and cardiac arrhythmias. Specifically, risk of systemic adverse events from tetracaine products includes (1) a systemic allergic response to p-aminobenzoic acid (PABA) which, at worst, could lead to cardiac arrest; or (2) excessive systemic absorption following repetitive or extensive application, especially for a 4% product, which could ultimately lead to convulsions. Tetracaine is associated with a higher incidence of allergic reactions than other anesthetics, such as lidocaine. The risk of systemic toxicity is greatest in small children and in patients with pre-existing heart disease. Factors that may increase systemic exposure are time and surface area of the exposure, particularly when the area of application is covered by an occlusive dressing. Benzocaine has an additional toxicity not seen with lidocaine, methemoglobinemia, an acquired decrease in the oxygen-carrying capacity of the red blood cells. Further, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations of local anesthetics because of their inability to metabolize them.

The Extra Strength Triple Anesthetic Cream compounded by your firm is a drug within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). This product is misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that its labeling fails to bear adequate directions for its use. It is not exempt from this requirement under 21 CFR § 201.115, because it is a new drug within the meaning of section 201(p) of the FDCA that lacks an approved application filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

Depending on its labeling, this product may also violate section 502(a) of the FDCA (21 U.S.C. § 352(a)). A drug or device is misbranded under section 502(a) if its labeling is false and misleading in any particular (e.g., if the labeling for your local anesthetic products fails to reveal the consequences that may result from the use of the product as a local anesthetic).

3. Repackaging:

Additionally, we are in receipt of a complaint alleging that you are repackaging the approved injectable drug, Avastin, into syringes for subsequent promotion and sale to health professionals. Avastin is unpreserved and is packaged and labeled in 4 and 16 ml single-use glass vials. The labeled precautions include "discard any unused portion left in a vial"

Each step in the manufacture and processing of a new drug or antibiotic, from handling of raw ingredients to final packaging, must be approved by FDA, whether carried out by the original manufacturer or by some subsequent handler or repacker of the product. Pharmacists are not exempt from these statutory requirements. Generally, the agency regards mixing, packaging, and other manipulations of approved drugs by licensed pharmacists, consistent with the approved labeling of the product, as an approved use of the product if conducted within the practice of pharmacy, i.e., filling prescriptions for identified patients. However, processing and repackaging (including repackaging) of approved drugs is beyond the practice of pharmacy and is thus subject to the Act's premarket approval requirements.

The agency has an established policy, articulated in Compliance Policy Guide Sec. 446.100, Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations (CPG 7132c.06) (copy enclosed), concerning the manipulation of approved sterile drug products outside the scope of the FDA-approval. FDA is particularly concerned about the manipulation of sterile products when a sterile container is opened or otherwise entered to conduct manipulations. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard are compromised and are no longer valid. We are especially concerned with the potential microbial contamination associated with splitting Avastin -- a single-use, preservative-free, vial -- into multiple doses. When used intravitreally, microbes could cause endophthalmitis, which has a high probability for significant vision loss. The absence of control over storage, and delays before use after repackaging, only exacerbate these concerns.

Avastin is approved for use in the treatment of colorectal cancers. The text of your alleged promotional material offers this drug to ophthalmologists. Avastin has no approved indications for use in the eye. As such, your firm is distributing an unapproved new drug in violation of section 505 of the FDCA. Because the product lacks adequate labeling for its intended use (see 21 CFR § 201.128) your firm is also distributing a misbranded drug in violation of section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)).

Also, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited. Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited.

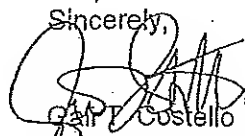
Further, we have been informed that, although your firm advises physicians that a prescription for an individually identified patient is necessary to receive compounded drugs, your firm has reportedly also told physicians' offices that using a staff member's name on the prescription would suffice. Drugs compounded in this manner are not compounded consistent with the CPG, and FDA will not exercise its enforcement discretion regarding those drugs.

The above violations are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice, including seizure or injunction against you and your firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of any steps that you will take to correct the noted violations, including an explanation of the steps taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time within which the correction will be complete.

You should address your reply to this letter to the U.S. Food and Drug Administration, New England District Office, One Montvale Ave., 4th Floor, Stoneham, MA 02180, Attn: Ann Simoneau, Compliance Officer. If you have any further questions, please feel free to contact Ms. Simoneau at (781) 596-7732.

Sincerely,



Gary Costello
District Director
New England District Office

cc: Charles R. Young, RPH
Executive Director
Massachusetts State Board of Pharmacy
239 Causeway Street, 5th floor
Boston, MA 02114

**October 31, 2008 FDA Response to NECC Letter
regarding FDA Warning Letter**



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

W.L. File

One Montvale Avenue
Stoneham, Massachusetts 02180
(781) 596-7700
FAX: (781) 596-7896

~~October 31, 2008~~

Mr. Barry J. Cadden, Director and Pharmacy Owner
New England Compounding Center
697 Waverly St.
Framingham, MA 01702

Dear Mr. Cadden:

This letter replies to your January 5, 2007 response to an FDA Warning Letter issued to your firm on December 4, 2006. We acknowledge and apologize for the significant delay in this correspondence.

Your letter asserts that the unapproved drug and misbranding charges in the Warning Letter do not apply because of the decision in *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006). You also state that your firm engages in "the kind of activity that the *Medical Center Pharmacy* court determined does not result in the introduction of new drugs into interstate commerce."

As stated in the Warning Letter, FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view is that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective" for their labeled uses. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"). There is substantial judicial authority supporting FDA's position that compounded drugs are not exempt from the new drug definition. See *Professionals & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) ("Although the [FDCA] does not expressly exempt 'pharmacies' or 'compounded drugs' from the new drug . . . provisions, the FDA as a matter of policy has not historically brought enforcement actions against pharmacies engaged in traditional compounding."); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd*, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs"

under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

As to your argument based on *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006), on July 18, 2008, the United States Court of Appeals for the Fifth Circuit issued a ruling in the case on appeal. *Medical Center Pharmacy v. Mukasey*, 536 F. 3d 383 (5th Cir. 2008). The Fifth Circuit rejected the finding by the United States District Court for the Western District of Texas that compounded drugs are exempt from the definition of "new drugs" in the FDCA. The Fifth Circuit concluded instead that compounded drugs are "new drugs." The court also ruled on the severability of advertising prohibitions in section 503A of the FDCA, which were found unconstitutional in a prior Supreme Court decision, *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).¹ The Fifth Circuit held that the restrictions on commercial speech in section 503A of the FDCA could be severed from the rest of 503A and that the remainder of 503A is valid and in force.

The Fifth Circuit's severability ruling conflicts with an earlier decision by the United States Court of Appeals for the Ninth Circuit, which held that the unconstitutional parts of section 503A are not severable and that all of section 503A is therefore void. *Western States Medical Center v. Shalala*, 238 F.3d 1090 (9th Cir. 2001). FDA has determined at this time that it will apply the non-advertising provisions of section 503A to entities covered by this provision that are located within the jurisdiction of the Fifth Circuit (i.e., Texas, Louisiana, and Mississippi) as well as to the plaintiffs that brought the *Medical Center Pharmacy* case. Elsewhere, including in Massachusetts, the agency will continue to follow the enforcement approach reflected in the Compliance Policy Guide (CPG) section 460.200 ["Pharmacy Compounding"] issued by FDA on May 29, 2002 (see *Notice of Availability*, 67 Fed. Reg. 39,409 (June 7, 2002)).

Your letter states that your firm does not introduce unapproved drugs into interstate commerce and does not need approved NDAs before dispensing its compounded medications. We disagree. As explained above, FDA regards compounded drugs as new drugs that require agency approval before they are introduced into interstate commerce. Your firm's compounded products lack this approval and therefore violate the FDCA.

Also as explained above, while compounded drugs violate the FDCA, FDA generally exercises enforcement discretion when they are the result of traditional pharmacy compounding. This discretion is contingent on factors such as the preparation of patient-specific drugs that meet medical needs for which FDA-approved drugs are unavailable.

¹ In 1997, Congress enacted, as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), a provision that related to pharmacy compounding, codified in section 503A of the FDCA (21 U.S.C. § 353a).

You state that you compound topical anesthetic formulas solely in accordance with formulas determined by the prescribing physicians. We acknowledge that you will require physicians to specify the chemical formulation on each patient-specific prescription for compounded topical anesthetic drugs. You also asked us to advise you whether using the term "triple anesthetic cream" to describe your compounded drug product is problematic. We find that use of this term implies the standardization of a compounded drug product rather than extemporaneous compounding for individually identified patients.

In the Warning Letter, FDA also expressed concern that you were generating sales for the "triple anesthetic cream" by providing physicians with "courtesy prescriptions" (i.e., free samples) of compounded drugs, without valid prescriptions that respond to patient-specific medical need, which would indicate the distribution by your firm of a standardized drug product. The development of a standardized drug product is inconsistent with the traditional practice of pharmacy compounding where pharmacists extemporaneously compound drugs upon receipt of valid prescriptions. In your response you assert that these "courtesy samples" are dispensed "only upon receipt of a valid prescription from a licensed practitioner to meet the unique medical needs of a particular patient" and that these are not samples as that term is defined in the Prescription Drug Marketing Act (PDMA). The Warning Letter did not allege that your practice violates the PDMA, and FDA does not take a position on this issue at this time. Nevertheless, we acknowledge your response that you provide a small amount of medication free of charge only upon receipt of a valid prescription. We will evaluate in a future inspection your current practices and any changes that you make to those practices and assess whether, despite these practices and changes, you produce standardized topical anesthetic products. We will not exercise enforcement discretion toward such products.

Please note that your letter does not alleviate our concern about the health risks associated with the topical anesthetics compounded by your firm. You state that "Virtually all drugs, including manufactured drugs, pose serious health risks if they are misused by physicians or patients." But the drugs compounded by your firm may be dangerous even if used as directed because they are extremely potent in comparison to FDA-approved topical anesthetic drugs. As noted in the Warning Letter, these risks are exacerbated if the safety-related information that accompanies these products is deficient.

We acknowledge that you have stated that you no longer dispense prescriptions for compounded products containing trypan blue or 20% aminolevulinic acid solution.

With regard to the repackaging of Avastin, we acknowledge your assertion that you repackage the product only upon receipt of a valid prescription from a licensed practitioner for an individual patient and your argument that this repackaging constitutes

the practice of pharmacy. However, each step in the manufacture and processing of a new drug, including packaging, must be approved by FDA, whether carried out by the original manufacturer or, in most cases, by a repackager. Pharmacists are not exempt from this requirement; however, FDA's Compliance Policy Guide on repackaging (Compliance Policy Guide Sec. 446.100, Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations) provides that the agency will exercise enforcement discretion toward pharmacists who repackage approved drugs within the practice of pharmacy for use consistent with the drug's approved labeling. Your repackaging is not consistent with Avastin's approved labeling, where you repackage the drug from vials into syringes, and where the labeled precautions include "discard any unused portion left in a vial...."

FDA is concerned about the manipulation of sterile products when a sterile container is opened or otherwise entered to conduct manipulations. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard(s) are compromised and are no longer valid. We are especially concerned with the potential microbial contamination associated with splitting Avastin—a single-use, preservative-free vial—into multiple doses. When used intravitreally, microbes could cause endophthalmitis, which has a high probability for significant vision loss. The absence of controls over storage, and delays before use and after repackaging, only exacerbate these concerns.

As stated in the Warning Letter, your repackaging is not consistent with Avastin's approved labeling; therefore, for the reasons stated in the warning letter, we believe that your firm is distributing an unapproved new drug in violation of section 505 of the FDCA and a misbranded drug in violation of section 502(f)(1) of the FDCA.

Finally, we acknowledge your concern about the time between our last inspection of your pharmacy and the issuance of the Warning Letter. We agree that the length of intervening period was unusual. This in no way diminishes our serious concerns about your firm's operation.

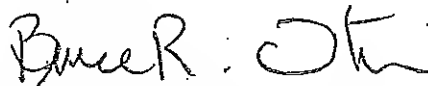
Your firm must promptly correct the violations noted in the December 4, 2006, Warning Letter, and establish procedures to assure that such violations do not recur. Its failure to do so may result in enforcement action, including seizure of the firm's products and/or an injunction against the firm and its principals.

In a future inspection, we will confirm the commitments that you made in your response. We also will verify that your firm's compounding practices are consistent with the policy articulated in the CPG, and that your firm's operation is not otherwise at odds with the conditions under which the agency exercises enforcement discretion toward's pharmacy compounding.

New England Compounding Center
Framingham, MA 01702
Page 5

Please direct any questions you have to Bruce Ota, Compliance Officer. U.S. Food and Drug Administration, New England District Office, One Montvale Ave., 4th Floor, Stoneham, MA 02180.

Sincerely,

A handwritten signature in dark ink, appearing to read "Bruce R. Ota". The signature is fluid and cursive, with the first name "Bruce" and last name "Ota" being clearly legible.

Bruce R. Ota
Compliance Officer
New England District Office

May 10, 2011 Email Forwarding CO Complaint to FDA

July 16, 2012 Email from FDA to Colorado

~~Martha, Susan~~

From: ~~Regina, Benita~~ <~~Regina.Benita@fda.hhs.gov~~>
Sent: Monday, July 16, 2012 2:54 PM
To: ~~Martha, Susan~~
Cc: ~~Wardwell, Amber~~; Ota, Bruce R; ~~Archibison, Karen M~~
Subject: FW: New England Compounding Center (NECC)
Attachments: Attachment - 1.pdf; Attachment - 2.pdf; Attachment - 3.pdf; hppsca45.pdf

Hi ~~Martha~~:

I checked our Registration database and New England Compounding Center is not listed as having registered with us as a manufacturer. With this e-mail, I am copying our New England District Compliance staff with the information you provided (Invoice for the Injectable hyaluronidase to Delta County Memorial Hospital) along with the Cease and Desist documents ~~Charles, Susan~~ sent last year regarding NECC (see e-mail string below). I would suggest you get in touch with the Massachusetts Board of Pharmacy if you haven't already to inform them of the firm's activity and to see if there are any actions they may wish to take especially in light of your Cease and Desist Order.

I also checked the status of Wedgewood Pharmacy in New Jersey. They also are not listed in our database as having registered as a manufacturer. Under a separate e-mail, I will copy our New Jersey District Office with the invoice you collected, but as in the NECC case, you may wish to contact your counterparts with the New Jersey Board of Pharmacy.

Let me know if you have any questions or wish to discuss further.

~~Regina~~
From: ~~Wardwell, Amber~~
Sent: Tuesday, May 10, 2011 3:07 PM
To: ~~Benita, Regina A~~; ~~Archibison, Karen M~~; Ota, Bruce R
Subject: FW: New England Compounding Center (NECC)

Thanks ~~Regina~~,

Bruce Ota is the CO for NECC. I'll ask him to follow up if we have any questions.

~~Amber~~

From: ~~Benita, Regina A~~
Sent: Tuesday, May 10, 2011 4:19 PM
To: ~~Wardwell, Amber~~; ~~Archibison, Karen M~~
Subject: FW: New England Compounding Center (NECC)

Hi ~~Amber~~ and ~~Regina~~:

I had a phone call with ~~Charles, Susan~~ of the Colorado Board of Pharmacy regarding New England Compounding Center (NECC). Attached is the background information from ~~Charles~~ as well as the Cease and Desist Order that the Board issued to NECC regarding their illegal distribution of compounded drugs to hospitals in the Denver metropolitan area. The firm is neither registered or listed with the State to do business as a drug outlet. I know that you have some previous reg history with this firm and that they were the recipient of at least one warning letter. This is just FYI but if you have any questions, please feel to give me a call to discuss.

~~Subject~~

From: ~~Charles, Chris~~ [mailto:~~Chris.Cameron~~@dora.state.co.us]
Sent: Tuesday, May 10, 2011 12:29 PM
To: ~~Brenda, Brenda A~~
Subject: New England Compounding Center (NECC)

Hi ~~Brenda~~,

Attachment – 1 is the report and exhibits that lead to the Cease and Desist Order;

Attachment – 2 is additional documents Pharmacy Board staff obtained at another facility (while related to NECC, it's unrelated to what actually led to the Cease and Desist Order); and

Attachment – 3 is the actual Cease and Desist Order.

As always, thanks for your help.

~~Chris~~

~~Chris Cameron~~
Chief Pharmacy Inspector
Colorado Department of
Regulatory Agencies
Division of Registrations
Board of Pharmacy
1560 Broadway, Suite 1500
Denver, CO 80202
P 303.733.1237 | F 303.733.1238



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THE COLORADO STATE BOARD OF PHARMACY
Special Report

Date: 13 April 2011

Inspector: Lisa A. Cornett

Subject: New England Compounding Center, Inc., OSP 5402

Issue: Unregistered/Unlicensed Distribution of Prescription Drugs Into Colorado

Details:

On 04/5/11, I conducted a routine inspection of Sky Ridge Medical Center, (PDO 168-01), 10101 Ridgeway Pkwy, Lone Tree, CO 80124. During the inspection, I collected records detailing the receipt of prescription drugs purchased from New England Compounding Center, Inc., PO Box 4146, Woburn, MA, 01888, a non-resident prescription drug outlet. This is a violation of CRS 12-22-130(2) and CRS 12-22-802(1).

BEFORE THE STATE BOARD OF PHARMACY

STATE OF COLORADO

Case No. 2011-3973

CEASE AND DESIST ORDER

IN THE MATTER OF THE UNAUTHORIZED AND UNLAWFUL DISTRIBUTION OF
PRESCRIPTION DRUGS AND/OR COMPOUNDED PRESCRIPTION DRUGS IN
COLORADO BY NEW ENGLAND COMPOUNDING CENTER, INC.,

Respondent.

Pursuant to guidance established by the Colorado State Board of Pharmacy ("Board") at its January 15, 2009 meeting, documentation has been considered, including, but not limited to, the written complaint dated April 13, 2011, 2011, in the above-captioned matter.

Based upon this review, the Board hereby finds that it has jurisdiction over Respondent and the subject matter herein, and that there exists credible evidence that Respondent has acted without the required license or registration, in violation of §12-22-130(2) and 12-22-802, C.R.S.

The Board finds as follows:

1. Respondent's location at 697 Waverly St, Framington, MA 01702 is licensed or registered with the Board as a nonresident prescription drug outlet to dispense and deliver prescription drugs and/or compounded prescription drugs in the State of Colorado pursuant only to valid, patient-specific prescription orders.

2. Respondent's location at 697 Waverly St, Framington, MA 01702 is not licensed or registered to distribute stock prescription drugs and/or compounded prescription drugs in the State of Colorado.

3. On or around January 17, 2011 and March 24, 2011, Respondent distributed a stock compounded prescription drug from 697 Waverly St, Framington, MA 01702 to a prescription drug outlet in the State of Colorado.

4. Respondent's conduct constitutes the unlawful distribution of prescription drugs into the State of Colorado, in violation of §12-22-130(2) and 12-22-802, C.R.S.

WHEREFORE, pursuant to §12-22-125.2(9), C.R.S., the Board hereby ORDERS that Respondent immediately CEASE AND DESIST in engaging in the unlawful distribution of prescription drugs in the State of Colorado, in violation of §§12-22-130(2) and 12-22-802, C.R.S.

Within ten days after service of this order to cease and desist, Respondent may request a hearing on whether such acts or practices in violation Article 22 of Title 12, C.R.S. have occurred. Such hearing shall be conducted pursuant to §§24-4-104 and 24-4-105, C.R.S.

The Board authorized the undersigned representative to sign this Cease and Desist Order on its behalf.

DATED this 15th day of April 2011.

STATE BOARD OF PHARMACY

BY: Wendy Anderson
Wendy Anderson
Program Director
1560 Broadway, Suite 1300
Denver, Colorado 80202

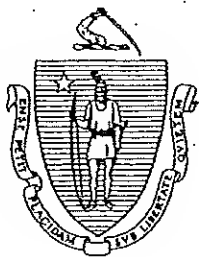
CERTIFICATE OF SERVICE

This is to certify that I have duly served the within CEASE AND DESIST ORDER upon all parties herein by depositing copies of same in the United States mail, first-class postage prepaid, at Denver, Colorado, this 15th day of April 2011, addressed as follows:

New England Compounding Center, Inc.
Attn: Designated Representative
697 Waverly St
Framington, MA 01702



*October 23, 2012 – Mass. Bd. Preliminary Investigation
Findings For NECC*



THE COMMONWEALTH OF MASSACHUSETTS
EXECUTIVE OFFICE OF HEALTH AND HUMAN SERVICES
Massachusetts Department of Public Health

New England Compounding Center (NECC)

Preliminary Investigation Findings

BOARD OF REGISTRATION IN PHARMACY REPORT

October 23, 2012

THE COMMONWEALTH OF MASSACHUSETTS
EXECUTIVE OFFICE OF HEALTH AND HUMAN SERVICES
DEPARTMENT OF PUBLIC HEALTH
PRELIMINARY INVESTIGATION REPORT - NECC 2012

INTRODUCTION

Since September 24, 2012 a widespread outbreak of fungal meningitis has affected people in 17 states and caused 23 deaths at the time of this report. The outbreak originated from a medication compounded by New England Compounding Center (NECC), a facility licensed by the Massachusetts Board of Registration in Pharmacy (Board). The Massachusetts Department of Public Health (DPH) has taken immediate action to protect public health and safety. In collaboration with investigators from the U.S. Food and Drug Administration (FDA), DPH investigators have worked to identify the root causes of these events. While the complete scope and severity of this outbreak will not be fully understood for many weeks, to ensure the utmost transparency, DPH is releasing these preliminary findings from its ongoing investigation of NECC. This report constitutes early findings that may be subject to revision as the investigation unfolds.

Medication compounding involves the practice of taking commercially available products and modifying them to meet the needs of an individual patient pursuant to a prescription from a licensed provider. Nearly all retail pharmacies in Massachusetts perform compounding, however only 25 compounding pharmacies meet the standards necessary to produce sterile injectable products. By terms of their license with the Board, every Massachusetts pharmacy must comply with Massachusetts laws and regulations, including compliance with the United States Pharmacopeia Standards. Compounding pharmacies may only perform compounding upon receipt of a patient-specific prescription. These requirements and restrictions are consistent with the rules in place in other states.

Upon beginning the joint on-site investigation of NECC early in this outbreak, DPH and FDA investigators identified serious deficiencies and significant violations of pharmacy law and regulations that clearly placed the public's health and safety at risk.

KEY FACTS

DATE(S) OF INVESTIGATION: *September 26, 2012 to Present*
PHARMACY LICENSE NUMBER AND INITIAL ISSUE DATE: *DS2848; July 16, 1998*
LICENSE STATUS: *Voluntary Surrender, October 3, 2012*
CORPORATION NAME: *New England Compounding Pharmacy, Inc.*
DBA NAME: *New England Compounding Center (NECC)*
ADDRESS: *697 Waverly Road, Framingham, MA, 01702*
MANAGER OF RECORD AND LICENSE NUMBER: *Cadden, Barry J; PH21239*
DEA REGISTRATION NUMBER AND EXPIRATION DATE: *BNS927819, July 31, 2013*
PRACTICE SETTING: *Specialty Pharmacy*
PREVIOUS INSPECTION DATE: *May 24, 2011*
PREVIOUS INSPECTION DOCKET OR STAFF ASSIGNMENT NUMBER: *ISP-738*

THE COMMONWEALTH OF MASSACHUSETTS
EXECUTIVE OFFICE OF HEALTH AND HUMAN SERVICES
DEPARTMENT OF PUBLIC HEALTH
PRELIMINARY INVESTIGATION REPORT - NECC 2012

INVESTIGATIVE METHODOLOGY

The NECC on-site investigation process consisted of DPH investigators obtaining documentary evidence (including photographs), reviewing and obtaining copies of Standard Operating Procedures, observational findings, reviewing and obtaining copies of all policies and procedures, reviewing batch records and interviewing NECC staff. The FDA conducted product testing and investigators took environmental samples of various areas of the facility to test for contaminants.

DPH investigators principally communicated with three NECC staff members during the on-site investigation (Barry J. Cadden, Glenn A. Chin and Lisa Conigliaro-Cadden) along with FDA investigators. After September 26, 2012, the majority of NECC employees were no longer on site. As has publicly been documented, NECC terminated many of their staff. The continuing investigation will include interviews of NECC employees.

SELECTED PRELIMINARY FINDINGS

During the facility inspections, investigators documented serious health and safety deficiencies related to the practice of pharmacy. All pertain to violations of 247 CMR 9.01(3) or 247 CMR 6.01(5)(a):

- NECC distributed large batches of compounded sterile products directly to facilities apparently for general use rather than requiring a prescription for an individual patient.
 - Records show that NECC had lists of potential patient names but did not have patient-specific prescriptions from an authorized practitioner when compounding and dispensing medication, as required by state law.
 - Manufacturing and distributing sterile products in bulk was not allowed under the terms of its state pharmacy license. If NECC was appropriately licensed as a manufacturer with the FDA the company would have been subject to additional levels of scrutiny.
 - NECC did not conduct patient-specific medication history and drug utilization reviews as required by regulations.

THE COMMONWEALTH OF MASSACHUSETTS
EXECUTIVE OFFICE OF HEALTH AND HUMAN SERVICES
DEPARTMENT OF PUBLIC HEALTH
PRELIMINARY INVESTIGATION REPORT - NECC 2012

- NECC distributed two of the recalled lots of methylprednisolone acetate (PF) 80 MG/ML prior to receiving results of sterility testing:
 - Lot 06292012@26 was prepared on June 29, 2012. Final sterility testing was completed on July 17, 2012. Two shipments of product were made prior to the final sterility tests results being received.
 - Lot 08102012@51 was prepared on August 10, 2012. Final sterility testing was completed on August 28, 2012. Eleven shipments of product were made prior to the final sterility tests results being received.
 - While NECC's records show the sterility tests found no contamination, the adequacy of NECC's sterility testing methods are currently under examination.
- Final sterilization of product did not follow proper standards for autoclaving (sterilization through high pressure steam) pursuant to United States Pharmacopeia Standard 797 (USP 797) and NECC's own Standard Operating Procedures:
 - Examination of NECC records indicated a systemic failure to keep products in the autoclave for the required minimum 20-minute sterilization period necessary to ensure product sterility.
- NECC did not conduct proper validation of autoclaves pursuant to USP 797:
 - NECC failed to test their autoclaves to ensure proper function.
- Visible black particulate matter was seen in several recalled sealed vials of methylprednisolone acetate from Lot 08102012@51.
- Powder hoods, intended to protect pharmacists from inhaling substances during medication preparation, within the sterile compounding area were not thoroughly cleaned pursuant to USP 797.
 - Residual powder was visually observed within the hood during inspection. This contamination may subsequently lead to contamination of compounded medications.
- Condition of "Tacky" mats, which are used to trap dirt, dust, and other potential contaminants from shoes prior to clean room entry, violated the USP 797.
 - Mats were visibly soiled with assorted debris.

THE COMMONWEALTH OF MASSACHUSETTS
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- A leaking boiler adjacent to the requisite clean room created an environment susceptible to contaminant growth:
 - A pool of water was visually observed around the boiler and adjacent walls, creating an unsanitary condition; the culture results of this potential contaminant are still pending.

CHRONOLOGY OF THE OUTBREAK & DEPARTMENT OF PUBLIC HEALTH ACTIONS

Monday September 24, 2012 – The Massachusetts Department of Public Health (DPH) was notified by Tennessee Department of Health in late evening about a cluster of six rare fungal meningitis cases, with onset of symptoms between July 30 and September 18, 2012. These patients had several risk factors in common, including an epidural injection of steroid (methylprednisolone acetate 80 mg/ml preservative free) compounded at New England Compounding Center (NECC) located in Framingham. Tennessee also reviewed three other products not made by NECC as potential contaminants.

Tuesday September 25, 2012 – DPH planned an investigation of NECC given growing concerns of linkage to infections. The DPH's Bureau of Health Care Safety and Quality, Board of Registration in Pharmacy (Board), and Bureau of Infectious Diseases began rapid response planning on September 25, and convened a multi-agency meeting between the Tennessee Department of Health, the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), and the New England Compounding Center (NECC). At the demand of DPH staff, Barry Cadden and Gregory Conigliaro, principal owners of NECC, immediately provided documentation of all facilities in the nation that had received medications from three lots of methylprednisolone acetate that were suspected by the CDC as being linked to the fungal infections ("suspect lots"). Distribution lists were provided to public health authorities across the country, including CDC and FDA. The suspected product was distributed to more than 14,000 patients in 23 states.

**Suspect Lots of Methylprednisolone Acetate (PF) 80 mg/ml Injection
identified by TN DOH:**

Lot #05212012@68 prepared by NECC on 5/21/2012
Lot #06292012@26 prepared by NECC on 6/29/2012
Lot #08102012@51 prepared by NECC on 8/10/2012

17,676 total doses

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Wednesday September 26, 2012 – DPH began an onsite investigation of NECC and instituted a recall of all suspect lots of methylprednisolone acetate. Investigators confirmed that all non-distributed methylprednisolone products were quarantined, and that methylprednisolone acetate was no longer being produced. Approximately 3,000 doses were quarantined or returned through recall. Upon arriving at NECC, investigators found NECC employees cleaning sterile compounding areas and conducting environmental testing. DPH investigators also detected signs of bleach decontamination in the compounding areas.

Thursday September 27, 2012 to Sunday September 30, 2012 – DPH coordinated with FDA to plan a collaborative investigation of NECC.

Monday October 1, 2012 – DPH and FDA began a joint investigation at NECC. Findings supported by the epidemiological work of the CDC prompted DPH to issue a formal Quarantine Notice pursuant to M.G.L. c. 94C, §§ 13 and 189A, and M.G.L. c. 112, §§ 30 and 42A. This legally formalized the September 26 quarantine action. The Notice directed that all methylprednisolone acetate raw materials (chemicals), all non-sterile and sterile products located at NECC used in the compounding of methylprednisolone acetate, and all inventory on the premises prepared for dispensing and stored at the pharmacy, or received by recall should be quarantined and not disposed of without the express approval of the DPH. Investigators were shown examples of methylprednisolone products that were labeled as patient specific. The associated documents were not individual prescriptions but lists of patients generated by a clinical facility and provided to NECC to obtain the product. NECC stated the list of names was considered to be an authorized prescription by the physician. This practice is not in accordance with Massachusetts regulations.

Tuesday October 2, 2012 – DPH and FDA observed visible black particulate matter in sealed vials (of purportedly sterile methylprednisolone acetate) returned to NECC. Inconsistencies in sterilization processes of materials were identified through review of NECC's records. The Board voted to obtain a Voluntary Surrender of NECC's license or to initiate action to issue a Temporary Order of Summary Suspension.

Wednesday October 3, 2012 – DPH secured voluntary surrender of NECC's license, effective 12 pm (noon), and instituted a voluntary recall of all intrathecal products (those injected into the area around

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the spinal cord or brain). DPH also notified Massachusetts providers to cease use of all NECC products.

Thursday October 4, 2012 – DPH and FDA publicly announced that black particulate matter, tentatively identified by microscopy as fungal contamination, was seen in a sealed, purportedly sterile vial of methylprednisolone acetate from a suspect lot. CDC and FDA recommended that all health care professionals cease use and remove from their pharmaceutical inventory any material produced by NECC. Massachusetts State Epidemiologists contacted nine Massachusetts health care facilities that received non-implicated lots of methylprednisolone acetate, instructing them to contact recipient patients to determine whether there were any unusual infections or other complications. No infections from the non-implicated lots sent to Massachusetts facilities have been identified at this time. DPH and FDA investigators continued with their on-site investigation and evaluated standard operation procedures and batch records related to sterile compounding. FDA investigators took environmental samples of various areas of the facility to test for contaminants.

Friday October 5, 2012 – DPH and FDA investigators noted visible contaminants in additional sealed recalled vials of methylprednisolone acetate. The particulate matter was noted in vials labeled in conformance with Massachusetts pharmacy regulations with patient-specific information. Additionally, particulate matter was noted in recalled vials that were labeled without patient-specific names, in clear violation of Massachusetts regulations. DPH and FDA each issued an alert to providers and facilities across the country stating the identification of particulate matter.

Saturday October 6, 2012 – DPH secured an immediate recall of all NECC products.

Monday October 8, 2012 – At the request of DPH, Barry Cadden and Glenn Chin, leaders at NECC, voluntarily ceased practice as pharmacists pending completion of the investigation.

Wednesday October 10, 2012 – Based on their shared ownership and leadership with NECC, DPH requested that Ameridose and Alaunus Pharmaceutical cease all pharmacy operations and any dispensing, manufacturing or wholesale distribution of any products starting at 3 p.m. on October 10 and continuing until 5 p.m. on October 22. DPH and FDA staff began an on-site investigation of Ameridose, a pharmacy, distributor and wholesaler regulated by the FDA. At the demand of DPH, Barry J. Cadden agreed to immediately resign as manager, director and from any other management

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position at NECC, Ameridose, and Alaunus. DPH began working with the Massachusetts Hospital Association to ensure that the supply chain of medications would not be disrupted. The Board issued an advisory to all pharmacies and pharmacists in Massachusetts emphasizing that all of their actions must be performed in accordance with the United States Pharmacopeia. The advisory also reiterated that state law requires compounding pharmacies and pharmacists to have a patient-specific prescription from an authorized practitioner when compounding and dispensing medication. Compounding pharmacies and pharmacists were required to submit an affidavit asserting that they are following state law in this regard.

Sunday October 14, 2012 – DPH staff began on-site investigation of Alaunus Pharmaceuticals, a wholesale distributor affiliated with Ameridose and NECC.

Monday October 15, 2012 – FDA issued an advisory that a patient may have acquired fungal meningitis from a different NECC steroid injection, triamcinolone acetonide. DPH epidemiologists began outreach to all 192 facilities in Massachusetts who received any NECC injectable products and supported providers in patient outreach. In addition, the FDA reported a transplant patient with an *Aspergillus fumigatus* infection who received a NECC cardioplegic solution during surgery. The CDC is actively working to confirm the presence of fungal contaminants in cardioplegic solutions. DPH asked Massachusetts providers to contact any patients who received any injectable product, including ophthalmic drugs or cardioplegia solutions prepared by NECC after May 21, 2012.

Thursday October 18, 2012 – FDA released definitive laboratory confirmation of the presence of fungal contaminants in sealed vials of methylprednisolone acetate in a suspect lot prepared by NECCDPH and FDA collected samples from sealed vials of completed product at Ameridose. Results are currently pending with the FDA.

Friday October 19, 2012 – DPH and FDA investigators scrutinized business practices of Alaunus Pharmaceuticals, and potential for inappropriate distribution of NECC or Ameridose products. At the request of DPH, Ameridose and Alaunus Pharmaceuticals extended their cessation of operations until November 5, 2012.

Monday October 22, 2012 – The Board authorized DPH staff to request voluntary permanent surrender of the licenses of Barry J. Cadden, Glenn A. Chin, and Lisa Conigliaro-Cadden, as well as

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NECC. If the three pharmacists and NECC do not comply, the Board authorized staff to proceed with permanent revocation. All three individuals are currently prevented from practicing as pharmacists, and would be so prohibited throughout the appeal process.

ONGOING INVESTIGATION

The Department's collaborative investigation with the FDA is comprehensive and will continue until investigators have all information needed to determine what, if any, further action should be taken against NECC and its leadership. This investigation also extends to NECC's business practices and environmental conditions surrounding the business, including the presence of a nearby recycling center that shares ownership with NECC. Investigators are also looking into NECC's corporate entity, including, but not limited to, corporate ownership and governance structures at both NECC and sister companies, Ameridose and Alaunus. DPH will analyze and incorporate all evidence and information gathered by the FDA and the Board of Registration in Pharmacy into a final, comprehensive report. This report will be presented to the Board of Registration in Pharmacy, which will determine appropriate regulatory sanctions under administrative law. DPH will also assist with any investigation, federal or state, that explores the actions of NECC and its principals. DPH will continue to support and cooperate with federal policymakers in addressing gaps in oversight of compounding pharmacies, including leaders on the U.S. Senate Health, Education, Labor, and Pensions Committee, and the U.S. House of Representatives Energy and Commerce Committee, and members of the Massachusetts Congressional delegation, including Congressman Ed Markey. DPH will also work closely with the Massachusetts General Court to explore state-specific policy solutions. Findings of these investigations will be used to inform these state and federal actions to address regulatory gaps within the quickly evolving compounding industry.

October 2012 – FDA Inspection Reports for NECC

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office 1 Montvale Ave, Stoneham, MA 02180

DATE(S) OF INSPECTION

10/1-2, 10/4-5, 10/9, 10/15, and 10/26/12

Tel: (781) 587-7500

Industry Information: www.fda.gov/oc/industry

FEI NUMBER

3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Barry J. Cadden, Owner

FIRM NAME

New England Compounding Pharmacy Inc., d/b/a New England Compounding Center

STREET ADDRESS

697 Waverly Street

CITY, STATE AND ZIP CODE

Framingham, MA 01702

TYPE OF ESTABLISHMENT INSPECTED

Compounding Pharmacy

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1. On 10/02/2012, we observed approximately eighty-three (83) vials out of a bin containing 321 vials of methylprednisolone acetate (preservative free) 80mg/mL from Lot #08102012@51 (shipped to customers between 8/17/12 - 9/25/12 per firm distribution data), a sterile injectable drug, to contain what appeared to be greenish black foreign matter. Seventeen (17) vials from the same bin of methylprednisolone acetate (preservative free) 80mg/mL were observed to contain what appeared to be white filamentous material.

The sterility sample taken by the firm consisting of one 5ml vial of bulk formulated methylprednisolone acetate (preservative free) from lot 08102012@51 resulted in a sterile result (lab analysis started 8/14/12 and reported 8/28/12). However, the FDA analysis of FDA Sample #693965, consisting of methylprednisolone acetate (preservative free) 80mg/mL, 1mL filled vials, from Lot #08102012@51 collected from the firm, confirmed the presence of viable microbial growth in 50/50 vials tested. One vial examined microscopically showed fungal morphological features.

2. Although the formula worksheets state the raw materials are sterile, the Pharmacy Director stated that the firm uses non sterile active pharmaceutical ingredients (APIs) and raw materials, with the exception of sterile water for injection, to formulate injectable suspensions including but not limited to preservative free methylprednisolone acetate and triamcinolone. During the inspection, we observed that the labeling for the methylprednisolone API and additional raw materials did not indicate that they were sterile. Samples were collected for analysis of the non-sterile API and 3 additional raw materials used in the formulation of methylprednisolone acetate. The firm provided no documentation or evidence to support that the steam autoclave cycle used to sterilize suspensions formulated using non-sterile API and raw materials is effective.

3. The firm's environmental monitoring program yielded the following microbial isolates (bacteria and mold) within Clean Room 1 and Clean Room 2, used for the production of sterile drug products, between January 2012 and September 2012. Firm personnel stated that the firm shuts off the air conditioning from 8:00 pm to 5:30 am nightly in the Clean Room.

Table #1: Surface Samples from ISO 6 (Class 1,000) Rooms

Location	Alert: 3 CFU		Date
	Result Bacteria	Result Mold	
Main Clean Room			
CR Bin 1 (polymyxin under station 1)	0	1	2/16/12
4 FLR (near hood 5)	10*	2*	2/23/12
2 FLR (near hood 3)	3	1	3/8/12

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EMPLOYEE(S) SIGNATURE

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DATE ISSUED

10/26/12

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office 1 Montvale Ave, Stoneham, MA 02180

DATE(S) OF INSPECTION

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Industry Information: www.fda.gov/oc/industry

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TO: Barry J. Cadden, Owner

FIRM NAME

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Location	Result Bacteria	Result Mold	Date
4 FLR (near hood 5)	2	2	3/15/12
Table 2	0	1 mold (3/4 of plate)*	3/29/12
1 FLR (near hood 1)	One hair with growth around it.		3/29/12
4 FLR (near hood 5)	OG*	0	4/5/12
CRBin1 (inside big ullne bin with omnipaque 240)	1	1	6/13/12
3 FLR (near horiz hoods)	OG*	0	6/13/12
3 FLR (near horiz hoods)	1	2	6/28/12
CRBin2 (front of tetracaine Hcl powder container)	0	OG mold*	7/5/12
Pass thru	0	1 small mold	7/26/12

Note: (*) indicates result over action level; OG indicates over growth

Table #2: Surface Samples of ISO 7 (Class 10,000) Rooms

Alert: 5 CFU

Action: 7+ CFU

Location	Result Bacteria	Result Mold	Date
Gown Room (Clean Room 1)			
8 FLR (GR/near hooks)	23*	0	2/16/12
GRmisc2 (vent arms)	13*	1*	2/16/12
GRmisc2 (empty plastic bag in empty bin)	19*	0	2/23/12
GRmisc1 (vent arms behind hand washer)	27*	0	2/23/12
7 FLR (gown room/entrance)	2*	11*	2/23/12
8 FLR (gown room/near hooks)	11*	4*	2/23/12
7 FLR (gown room/entrance)	0	1	3/1/12
WallGR2 (windowsill slide to MR)	18*	0	3/1/12
8 FLR (gown room/near hooks)	12*	0	3/1/12
GRmisc2 (vent grids)	16*	2*	3/1/12
7 FLR (gown room/entrance)	3	2	3/8/12
8 FLR (gown room/near hooks)	3	2	3/8/12
7 FLR (gown room/entrance)	3	3	3/15/12
8 FLR (gown room/near hooks)	0	2	3/15/12
8 FLR (gown room/near hooks)	16*	0	3/29/12

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES
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DATE(S) OF INSPECTION

10/1-2, 10/4-5, 10/9, 10/15, and 10/26/12

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FIRM NAME

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Location	Result Bacteria	Result Mold	Date
GRmisc2 (floor under barrel against wall)	11*	0	3/29/12
8 FLR (gown room/near hooks)	10*	0	4/5/12
7 FLR (gown room/entrance)	0	1	4/5/12
GRmisc1 (rubber flap over wheel of rack)	9*	0	4/12/12
WallGR1 (window sill side to middle room)	9*	0	4/12/12
GRmisc1 (top of rack with bouffants)	12*	0	5/10/12
7 FLR (GR/entrance)	2	1	5/31/12
8 FLR (GR/near hooks)	19*	0	5/31/12
8 FLR (GR/near hooks)	0	13*	6/28/12
7 FLR (GR entrance)	3	3	6/28/12
GRmisc1 (bottom of bootie bin)	¼ of plate OG*	1*	7/26/12
GRmisc2 (bottom of mask bin)	plate ¼ overgrown*	0	7/26/12
8 FLR (GR/near hooks)	9*	0	7/26/12
GRmisc2 (front of 7-7.7 glove bin)	OG*	1*	8/2/12
GRmisc2 (loose bootie bin)	0	Plate ¼ mold*	8/23/12
Middle Room (Clean Room 1)			
5 FLR (near crimp bench)	0	1	2/23/12
6 FLR (near sink bench)	0	3	2/23/12
6 FLR (near sink bench)	2*	11*	3/15/12
MRmisc1 (dh20 gallon)	1	1	5/10/12
Gown Room (Clean Room 2)			
Gown Room Flr	OG*	0	1/26/12
Gown Room Flr	0	1	3/1/12
Gown Room Flr	9*	0	8/9/12
Prep Room (Clean Room 2)			
Prep Room Flr	1	1	2/2/12
Misc #2 PR (top of radio)	0	1	2/7/12
Misc: PR (Calcium chloride bin)	1	1	4/4/12
Prep Room Flr	15*	2*	6/13/12

Note: (*) indicates result over action level; OG indicates over growth

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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New England District Office 1 Montvale Ave, Stoneham, MA 02180

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Table #3: Surface Samples of ISO 8 (Class 100,000) Rooms
Alert: 8 CFU Action: 10+ CFU

Location	Result Bacteria	Result Mold	Date
Prep Room (Clean Room 1)			
Misc. Prep room samples (shopping cart handle)	0	OG with mold*	1/6/12
Misc. Prep room samples (metal cart)	1	1	1/26/12
PR (carriage w/blue handle w/scratch marks)	3	1	2/2/12
PR (carriage w/blue handle w/x)	4	1	2/2/12
PR (outside of barrel)	16*	2*	3/1/12
9 FLR (PR) (near entrance)	1	7	3/8/12
PR (blue tamper evident caps, bin)	4	3	3/15/12
PRmisc2 (inside plastic cover to clear plastic bags)	OG*	0	4/5/12
9 FLR prep room (near entrance)	¼ plate OG*	0	4/5/12
10 FLR (PR) (under 2 nd rack)	3	1	4/12/12
PR MISC 2 (top of lid of white container under rack)	1	1	5/24/12
10 FLR (PR) (back of room area)	OG*	0	5/24/12
10 FLR (PR) (back of room area)	0	3	5/31/12
9 FLR (PR) (entrance area)	OG*	0	6/15/12
10 FLR (PR) (back of room area)	20*	0	6/15/12
10 FLR (PR) (back of room area)	12*	0	6/28/12
9 FLR (PR) entrance area	4*	15*	6/28/12

Note: (*) indicates result over action level; OG indicates over growth

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Table #4: Air Sampling of ISO 6 (Class 1,000) Rooms

Location	Result Bacteria	Result Mold	Date
Middle Room (Clean Room 2)			
Middle room	0	1 big mold	5/29/12

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10/16/12

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Table #5: Air Sampling of ISO 7 (Class 10,000) Rooms

Alert: 5 CFU

Action: 8+ CFU

Location	Result Bacteria	Result Mold	Date
Gown Room (Clean Room 1)			
Gown room	29*	1*	5/31/12
Gown room	11*	1*	6/28/12
Middle Room (Clean Room 1)			
Crimp Station	3	1	2/23/12
Prep Room (Clean Room 2)			
Prep room	0	1	5/2/12
Gown Room (Clean Room 2)			
Gown room	7*	3*	8/9/12

Note: (*) indicates result over action level

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ORIGINAL -
NOT A
REDACTION

Table #6: Surface and Air Sampling of ISO 5 (Class 100) Clean Room 2

No Action/Alert Levels specified by firm for ISO 5 (Class 100) areas.

Location	Sample Type	Result Bacteria	Result Mold	Date
Table 1 (near Horiz L & R hoods)	Surface	0	3	1/26/12
Table 1 (near Horiz L & R hoods)	Surface	1	1	5/2/12
Between Horiz L & Horiz R	Air	1	1	7/25/12

There was no investigation conducted by the firm when levels exceeded their action limits and there was no identification of the isolates. No documented corrective actions were taken to remove the microbial contamination (bacteria and mold) from the facility.

SEE
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PAGE

EMPLOYEE(S) SIGNATURE

Thomas W. Nerney, Investigator
Stacey S. Degarmo, Investigator
Philip Kreiter, Investigator
Almaris N. Alonso, Microbiologist
Debra M. Emerson, Investigator

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Stacey S. Degarmo, Investigator
Philip Kreiter, Investigator
Almaris N. Alonso, Microbiologist
Thomas W. Nerney, Investigator
Debra M. Emerson, Investigator

DATE ISSUED

7/31/12

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
New England District Office 1 Montvale Ave, Stoneham, MA 02180

DATE(S) OF INSPECTION
10/1-2, 10/4-5, 10/9, 10/15, and 10/26/12

Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

FEI NUMBER
3003623877

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Barry J. Cadden, Owner

FIRM NAME

New England Compounding Pharmacy Inc., d/b/a New England Compounding Center

STREET ADDRESS

697 Waverly Street

CITY, STATE AND ZIP CODE

Framingham, MA 01702

TYPE OF ESTABLISHMENT INSPECTED

Compounding Pharmacy

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

4. The environmental monitoring procedure requires sampling via personnel touch plates taken upon completion of sterile compounding and prior to cleaning. Records from January thru September 2012 for Clean Room 1 and Clean Room 2 showed the following results inside production hoods:

Table #1: Clean Room 1 and Clean Room 2 Facility Personnel Touch Plates

Date	Isolates	Location	Product
1/3/12	OG with bacteria	Horizontal 1 (Clean Room 1)	Avastin
4/12/12	OG with bacteria	IT/Hood 3 (Clean Room 1)	Product not documented
6/15/12	1 bacteria, 1 mold	Horizontal 2A (Clean Room 1)	Ropiv/Ketor/Epl
6/21/12	2 bacteria	Horizontal R (Clean Room 2)	Product not documented
7/2/12	1/2 plate OG with bacteria	Horizontal L (Clean Room 2)	Product not documented
7/19/12	1 bacteria, 2 molds	Horizontal 2C (Clean Room 1)	Mafenide Acetate
7/31/12	2 bacteria	Horizontal 2A (Clean Room 1)	KCl/Lido/DSW
8/16/12	2 bacteria	Hood-3 (glovebox) (Clean Room 1)	Ace 20%, Ped Atropine

Note: OG indicates over growth

These results were not investigated and there was no identification of the isolates. There were no product impact assessments performed for any sterile products that were made in the hoods or gloveboxes on the days the samples were taken. In addition, the firm has no evidence that any corrective actions were taken to prevent contamination of the sterile drug products.

5. The conditions listed below were identified during the inspection in areas used for the preparation, filling, and/or storage of sterile drugs products.

- On 10/04/2012, we observed condensation and what appeared to be tarnished discoloration on the interior surfaces (e.g. chamber) of the (b) (4) autoclave, located in the firm's Middle Room (ISO 7). This autoclave is used for the steam sterilization of formulated bulk drug suspensions, including preservative free formulations of methylprednisolone and triamcinolone, which are intended for injection. Of note, this is the final sterilization step in the process for these products.

SEE
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PAGE

EMPLOYEE(S) SIGNATURE

[Handwritten signatures]

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Stacey S. Degarmo, Investigator
Phillip Kreiter, Investigator
Almaris N. Alonso, Microbiologist
Thomas W. Nemej, Investigator
Oebra M. Emerson, Investigator

DATE ISSUED

10/26/12

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

New England District Office 1 Montvale Ave, Stoneham, MA 02180

DATE(S) OF INSPECTION

10/1-2, 10/4-6, 10/9, 10/15, and 10/26/12

Tel: (781) 587-7500 Industry Information: www.fda.gov/oc/industry

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

- On 10/04/2012, we observed greenish yellow discoloration lining the interior surface of the viewing lens within the "Inside" autoclave, located in the firm's Middle Room (ISO 7). This is one of two tabletop autoclaves used for steam sterilization of various components and equipment (e.g. vials of multiple sizes, stoppers, and spin bars) used in the formulation of sterile drug products
- On 10/04/2012, we observed what appeared to be tarnished discoloration on the interior surfaces (e.g. chamber and trays) of the "Outside" autoclave located in the firm's Middle Room (ISO 7). Moreover, condensation was observed along the interior surfaces of the "Outside" autoclave to collect in a pool at the base of the chamber. This is one of two tabletop autoclaves used for steam sterilization of various components and equipment (e.g. vials of multiple sizes, stoppers, and spin bars) used in the formulation of sterile drug products.
- The firm is abutted to the rear and along the left parking area by a recycling facility that handles such materials as mattresses and plastics. On 10/02/2012, the area was observed to include large equipment (e.g. excavators and freight trucks) producing airborne particulates (e.g. dust). Rooftop units serving the firm's HVAC system were estimated to be located approximately 100 feet from the recycling facility.
- On 10/04/2012, we observed what appeared to be dark particulate and white, filamentous substances covering the louvers of an HVAC return located behind the (b) (4) autoclave, located in the firm's Middle Room (ISO 7). This autoclave is used for the steam sterilization of formulated bulk drug suspensions, including preservative free formulations of methylprednisolone and triamcinolone, which are intended for injection.
- On 10/02/2012 and 10/04/2012, we observed yellow residue lining the rear return of Weigh Station 2 Hood and greenish residue lining the rear return of Weigh Station 3 Hood, both located in the firm's ISO 6 Clean Room. The firm uses Weigh Station Hoods to weigh active ingredients and other raw materials utilized in the formulation of sterile drug preparations.
- On 10/04/2012, we observed greenish residue covering the surface of the (b) (4) ceiling, exposed to the (b) (4) filter above, within Weigh Station 3 Hood located in the firm's ISO 6 Clean Room. The firm uses Weigh Station Hoods to weigh active ingredients and other raw materials utilized in the formulation of sterile drug preparations.
- On 10/04/2012, we observed what appeared to be tarnished discoloration on the interior surfaces (e.g. chamber and trays) of the (b) (4) located in the firm's Prep Room (ISO 8). This (b) (4) is used to sterilize equipment (e.g. beakers, spatulas, and spoons) used in the formulation of sterile drug products.

SEE
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EMPLOYEE(S) SIGNATURE

Stacey S. Degarmo, Investigator
Philip Kretler, Investigator
Almaris N. Alonso, Microbiologist
Thomas W. Nemey, Investigator
Debra M. Emerson, Investigator

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Stacey S. Degarmo, Investigator
Philip Kretler, Investigator
Almaris N. Alonso, Microbiologist
Thomas W. Nemey, Investigator
Debra M. Emerson, Investigator

DATE ISSUED

10/26/12

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
New England District Office 1 Montvale Ave, Stoneham, MA 02180

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

- On 10/04/2012, a boiler installed within approximately 30 feet of the entrance to the Prep Room (ISO 8) was observed to be leaking water into puddles. Moreover, wet floor surfaces around the boiler appeared to be soiled with thick white debris and thick black, granular material. Gaps were observed between sliding doors, located at the transition between the Prep Room (ISO 8) and the warehouse, despite being fully closed. This room is used for the preparation of equipment and includes the (b) (4).
- On 10/02/2012, the tacky mat located within the entrance of the Prep Room (ISO 8), at the transition to the warehouse, was observed to be brown and soiled. This room is used for the preparation of equipment and includes the (b) (4).
- On 10/04/2012, we observed cloudy discoloration on the (b) (4) barrier (b) (4) facing the ISO 6 Clean Room, and metal surfaces within the "Pass Thru," installed within the wall of the ISO 6 Clean Room. Moreover, the metal ledge, within the ISO 6 Clean Room, was observed to contain reddish-brown and cloudy substances. The firm utilizes the ISO 6 Clean Room to formulate and fill sterile preparations, including methylprednisolone.
- On 10/04/2012, we observed what appeared to be dark, hair-like discoloration along the gasket and crevices located at the bottom edge of the closed pass through installed within the wall of the ISO 6 Clean Room. The firm utilizes the ISO 6 Clean Room to formulate and fill sterile preparations, including methylprednisolone.

SEE
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EMPLOYEE(S) SIGNATURE

[Signature]
[Signature]
[Signature]

EMPLOYEE(S) NAME AND TITLE (Print or Type)

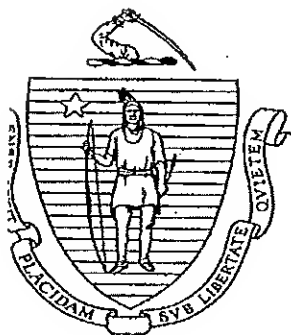
Stacey S. Degarmo, Investigator
Philip Kröller, Investigator
Almaris N. Alonso, Microbiologist
Thomas W. Nemej, Investigator
Dabra M. Emerson, Investigator

DATE ISSUED

11/26/12

Ameridose, LLC –

**Application for a New Store – 50 Fountain
Street (2006)**



The Commonwealth of Massachusetts
Executive Office of Health and Human Service
Department of Public Health
Division of Health Professions Licensure

Board of Registration in Pharmacy
239 Causeway Street, Suite 200, 2nd Floor
Boston, MA 02114
(800) 414-0168 (office) / 617-973-0983 (fax)
<http://www.mass.gov/reg/boards/ph>

APPLICATION FOR A NEW STORE

MTT ROMNEY
GOVERNOR
KERRY HEALEY
LIEUTENANT GOVERNOR
TIMOTHY R. MURPHY
SECRETARY
PAUL J. COTE, JR.
COMMISSIONER
JAMES P. DIKAS
DIRECTOR

APR 25 2006

BOARD OF
PHARMACY

APPROVED

5/10/06 BOARD
MEETING REVIEW

DATE: 5/10/06

SUBJECT TO COMPLIANT INSPECTION
& WAIVER APPROVED BY BOARD

3467 7/13/06

X

I hereby apply for a permit to operate a store for the transaction of retail drug business in accordance with the provisions of Chapter 112, General Laws.

\$351.00 licensure / application fee. Make check or money order for \$351.00 payable to the Commonwealth of Massachusetts. This fee is non-refundable.

1. Legal Name of Business. Ameridose, LLC
2. Full Business Address (Street Address, City, State and Zip). 50 Fountain Street, Framingham, MA 01702
3. Area Code and Telephone Number. 508-656-2653
4. All trade or business names ("D.B.A." names) used by same Corporation or by License. Ameridose, LLC
5. Type of ownership or operation (i.e., sole proprietorship, partnership, corporation). Limited Liability Company (LLC)
If corporation, please submit articles of corporation. Please see Attachment "A"
5. Names(s) and Social Security Number(s) of the owner(s) and/or operator(s) of the licensee. Please indicate type of ownership - Partnerships: the name of each partner and name address of partnership;

Corporations: the name and title of each corporate officer and director, the corporate names, name and address of parent company, if any, and the State of incorporation; Sole Proprietorship: the name of the sole proprietor and the address of the business entity. Please see Attachment "B"

7. Name of registered pharmacist charged with the management of the pharmacy. Sophia Pasedis, RPh, PharmD.
8. Registration number of above manager. 20217
9. Name(s) and registration number(s) of staff pharmacist(s) employed at pharmacy. Sophia Pasedis, RPh, PharmD.
10. Have any of the applicant(s) and/or managers-in-charge had: 1) any convictions related to the distribution of drugs (including samples); 2) any felony convictions; 3) any suspension(s) or revocation(s) or other sanction(s) by federal, state or local governmental agency of any license or registration currently or previously held by the applicant or license for the manufacture, distribution, or dispensing of any drugs, including controlled substances? NO

Have any applications for licensure been denied by any federal or state agency including any state board of pharmacy? NO

List and explain. Attach additional sheets if necessary. N/A
11. The applicant/licensee must notify the Board in writing of any changes in ownership or management within thirty (30) days of such change(s).
12. Social Security Number (Mandatory). [REDACTED]
Pursuant to M.G.L. c. 62C, s. 47A, the Division of Registration is required to obtain your social security number and forward it to the Department of Revenue. The Department of Revenue will use your social security number to ascertain whether you are in compliance with the tax laws of the Commonwealth.

List any licenses/certifications you hold in the United States or any country or foreign jurisdiction and the state/jurisdiction from which the license/certification was originally issued. Please attach a certificate of standing from each state or jurisdiction in which you are licensed/certified, indicating the status of your license and any relevant disciplinary information. Massachusetts Registered Pharmacist License #20217, Attachment "C."
14. Has any disciplinary action been taken against you by a licensing/certification board located in the United States or any country or foreign jurisdiction? Yes: ☐ No: ☒
If yes, please state the details (use a separate sheet if necessary). N/A
15. Are you the subject of pending disciplinary actions by a licensing/certification board located in the United States or any country or foreign jurisdiction? Yes: ☐ No: ☒
If yes, please state the details (use a separate sheet if necessary). N/A
16. Have you ever voluntarily surrendered or resigned a professional license to a licensing/certification board in the United States or any country or foreign jurisdiction? Yes: ☐ No: ☒
If yes, please state the details (use a separate sheet if necessary). N/A
17. Have you ever applied for and been denied a professional license in the United States or any country or foreign jurisdiction? Yes: ☐ No: ☒
If yes, please state the details (use a separate sheet if necessary). N/A

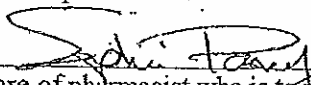
18. Pursuant to Board Regulations at 247CMR § 6.01(3), The Board shall not register nor permit ownership of a pharmacy or pharmacy department by a practitioner with prescriptive privileges. By signing this application the applicant certifies that none of the owners, directors or officers have prescriptive privileges.

Affidavit (must be completed and notarized)

Pursuant to M.G.L. c. 62C, s. 49A, I certify under the penalties of perjury that I, to the best of my knowledge and belief, have filed all state tax returns and paid all state taxes required under law.


The applicant certifies that each person employed in any prescription drug distribution activity has the education, training, and experience, or any combination thereof, sufficient for that person to perform the assigned functions in such a manner as to provide assurance that the drug product quality, safety, and security will at all times be maintained as required by law.

I hereby state that I am the person authorized to sign this application for all licensure; that all statements are true and correct in all respects and are made under the penalties of perjury.



Signature of pharmacist who is to manage the pharmacy or pharmacy department

¹⁴
April 5, 2006
Date


Social Security Number of the Manager of Record

Sworn and subscribed before me this 14th day of April, 2006

My commission expires 12/31/2010. Carrie Lee Alexander
Notary Public

To be completed by the Board: Check \$ 351 Date 5/2/06 Number 6170

Food and Drug Administration Establishment Inspection Report

Date Assigned: 09/27/2007 Inspection Start Date: 12/07/2007 Inspection End Date: 12/10/2007
 Firm Name & Address: Ameridose LLC, 50 Fountain St Framingham, MA 01702-6211 US
 Mailing Address:
 FEI: 3005881167 JD/TA: 13 County: MIDDLESEX Est Size: 25,000,000 - 49,999,999
 Phone: (508)656-2653 District: NWE-DO Profiled: Yes
 Conveyance Type: % Interstate: 90 Inspectional Responsibility: Field

Endorsement

PURPOSE: An inspection of this firm was conducted with investigators Massachusetts Board of Pharmacy as directed by the May 22, 2007 Inspection Request from HFD-317 Div of New Drugs and Labeling Compliance under PAC 56D015 and FACTS assignment#843994.

HISTORY: The firm, a limited liability corporation, opened in July, 2007 and drug registered with USFDA, stamped July 13, 2006, as repacker and other of sterile and nonsterile mixtures and Admixtures. The firm reregistered June 15, 2007. The firm was told to get a State of Mass Drug Manufacturers registration which it did dated June 6, 2007. The firm is also registered in Massachusetts as a retail pharmacy, and has DEA Licenses as a manufacturer and retail pharmacy for controlled substances. Mr. Barry J. Cadden, Director, and Mr. Gregory Conigliaro, General Manager, are listed on the drug registration under owners, partners or officers.

CURRENT FINDINGS: This is the initial inspection of the firm and is a fact finding inspection where 28 Pharmacy Compounding questions were asked of management and an inspectional tour of the facility was made to determine the firm's operations and its adherence to USP 797, the Food Drug and Cosmetic Act, and Compliance Policy Guide Section 460.200 Pharmacy Compounding. The inspection revealed that the firm has made over 610 Lots of products and 38 batches of products of Admixtures for hospitals and packaged them into IV bags, syringes and vials since they opened in 2006. The articles the firm mainly orders for its operations are: sterile actives, diluents bags, and syringes for their compounding and manufacture of admixtures operations. Some packaging is also done in cassettes and vials to accommodate the instruments used in some hospitals. They have ordered 15 different nonsterile powders which they reconstitute into large volume sterile stock solutions that are finished product tested and then used in Admixtures made for hospitals.

Number of Observations was issued at the conclusion of the inspection; however, a discussion was held at which time I discussed the formula Worksheets (batch records) and their content, SOPs, a reject bin containing labels, validation and verification of 32 different single ingredient and combination products, annual stability tests required on products, and annual product reviews.

ACTION ON PREVIOUS DEFICIENCIES: N/A

ACTION: NAI. Refer to HFD-310 Pharmacy Compounding Survey.

Distribution: O: NWE/DO CF (w/ex); cc: HFD-310 (w/ex), FMD-145 (Compl), e/s: SAS, RHP, GJH, RF.

Endorsement Location: FACTS and NWE/DO CF

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
Richard H Penta	01/16/2008 02:02 PM ET	Gary J Hagan	01/22/2008 09:24 AM ET

Food and Drug Administration Establishment Inspection Report

FBI:300588I167

Inspection Start Date: 12/07/2007

Inspection End Date: 12/10/2007

Firm Name & Address: Ameridose LLC, 50 Fountain St Framingham, MA 01702-6211 US

Related Firm FBI:

Name & Address of Related Firm:

Registration Type

DRG Drug

Registration Dates

04/01/2007

05/01/2006

Establishment Type

M Manufacturer

R Repacker/Packer

Industry Code

65 Human and Animal Drugs

60 Human and Animal Drugs

District Use Code:

Food and Drug Administration Establishment Inspection Report

FEI: 3005881167

Inspection Start Date: 12/07/2007

Inspection End Date: 12/10/2007

Firm Name & Address: Ameridose LLC, 50 Fountain St Framingham, MA 01702-6211 US

Inspection Basis: Surveillance

Inspected Processes & District Decisions

PAC	Establishment Type	Products/ Process	MQSA Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56D015	Manufacturer	65 D C N			No Action Indicated (NAI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	01/10/2008	No Action Indicated (NAI)	Penta, Richard H	NWE-DRUGS

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	01/22/2008	No Action Indicated (NAI)	Hagan, Gary J	NWE-DRUGS

Remarks:

PAC	Establishment Type	Products/ Process	MQSA Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
56D015	Manufacturer	65 R C N			No Action Indicated (NAI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	01/14/2008	No Action Indicated (NAI)	Penta, Richard H	NWE-DRUGS

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	01/22/2008	No Action Indicated (NAI)	Hagan, Gary J	NWE-DRUGS

Remarks:

Food and Drug Administration Establishment Inspection Report

FEI: 3005881167

Inspection Start Date: 12/07/2007

Inspection End Date: 12/10/2007

Establishment Name & Address: Ameridose LLC, 50 Fountain St Framingham, MA 01702-6211 US

Products Covered

Product Code	Est Type	Description	Additional Product Description
65 D C N 06	Manufacturer	Oxytocin (Injection) (Oxytocic); Human - Rx/Single ingredient; Large Volume Parenteral >= 100ml	
65 R C N 14	Manufacturer	Potassium Chloride (Replenisher); Human - Rx/Single Ingredient; Large Volume Parenteral >= 100ml	

Assignees Accomplishment Hours

Employee Name	Position Class	Hours Credited To	PAC	Establishment Type	Process	Hours
Penta, Richard H	INV	NWE-DO	56D015	Manufacturer	65 D C N	56
Penta, Richard H	INV	NWE-DO	56D015	Manufacturer	65 R C N	15
Total Hours:						71

Food and Drug Administration Establishment Inspection Report

FEI: 3005881167

Inspection Start Date: 12/07/2007

Inspection End Date: 12/10/2007

Establishment Name & Address: Ameridose LLC, 50 Fountain St Framingham, MA 01702-6211 US

Inspection Result

EIR Location
Turbo & NWE/DO CF

Trips Num

Inspection Summary

IB Suggested Actions

Action	Remarks
--------	---------

Referrals

Org Name	Mail Code	Remarks
CDER-DNDLC	HFD-310	Compounding Pharmacy Survey

Refusals

Inspection Refusals: No refusal

Samples Collected

Sample Number

Recall Numbers

Recall Number

Related Complaints

Consumer Complaint Number

FDA 483 Responses

483 Issued?:

483 Location:

Response Type	Response Mode	Response Date	Response Summary
---------------	---------------	---------------	------------------



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Division of Health Professions Licensure
239 Causeway Street, Suite 200
Boston, MA 02114

Office of Public Protection
(617) 973-0865 Fax (617) 973-0985 TTY (617)-973-0895

INSPECTION REPORT

Date of Inspection 11/19/08 Reg. No. Pending Expiration Date _____

Purpose of Inspection New Location ☒ Relocation _____ Compliance _____

Docket No. OR Staff Assignment No. 20080917 DS 031

Corporation Name _____

Pharmacy DBA Name Ameri-dox LLC Store No. _____

Address 205 Flinders Rd Westborough 01581

Telephone No. 888-820-0622 Fax No. 508-820-0644

Manager of Record Steve Perry Reg. No. 17303

Pharmacy DEA Registration No. and Expiration Date Pending

Pharmacy Hours. Daily 6 - 8 Saturday 6 - 6 Sunday _____

Practice Setting Community Chain _____ With Drive-thru Window _____
Community Independent _____ Specialty ☒ Long Term Care _____

Daily Pharmacy Volume Less than 100 _____ 100 to 500 _____ Above 500 _____

Staff Pharmacists (Names and Registration Numbers)

Pharmacy Interns (Names and Registration Numbers)

Pharmacy Technicians (Names, Registration Numbers and Certification Status)

TBD

Other Pharmacy Support Staff and Trainees (Names and positions)

TBD

SECURITY - 247 CMR 6.02 and CFR 1301.75(b)	YES	NO
ADEQUATE SECURITY SYSTEM	✓	
EVIDENCE OF SECURITY CAMERAS	✓	
SECURITY BARRIER SEPARATES PHARMACY DEPARTMENT	✓	
PROCEDURE FOR ABSENCE OF PHARMACIST	✓	
CONTROLLED SUBSTANCES ARE LOCKED IN A SECURE CABINET	✓	
CONTROLLED SUBSTANCES ARE DISPERSED THROUGHOUT GENERAL INVENTORY	✓	
LOSS OR THEFT OF CONTROLLED SUBSTANCES (DEA FORM 106) REPORTED TO THE BOARD	✓	
SECURITY/ACCESS TO PHARMACY RESTRICTED TO AUTHORIZED PERSONNEL	✓	
COMMENTS: <i>Regulations Reviewed</i>		

LICENSURE/REGISTRATION STATUS OF PHARMACY STAFF	YES	NO
COPIES OF PHARMACIST LICENSES ARE POSTED AND CURRENT	✓	
COPIES OF TECHNICIAN REGISTRATIONS ARE CURRENT AND AVAILABLE	✓	
PROCEDURES IN PLACE TO MAINTAIN PATIENT CONFIDENTIALITY WITH REGARD TO DISCARDED PRESCRIPTION INFORMATION (e.g. SHREDDER)	✓	
COMMENTS: <i>Regulations Reviewed</i>		

STANDARDS FOR PRESCRIPTION LABELING AND FORMAT M.G.L. c. 94C, § 21 and CMR 721.000	YES	NO
PHARMACIST INITIALS ON LABEL AND SERIAL NO. OF RX	✓	
"BEYOND USE" DATE IS SHOWN ON LABEL	✓	
INVENTORY LABELED WITH BRAND, OR GENERIC NAME AND MANUFACTURER, STRENGTH, LOT NUMBER, EXPIRATION DATE, OR INTERNAL CONTROL NUMBER WHICH REFERENCES MANUFACTURER AND LOT NUMBER USED	✓	
LABEL COMPLIANT WITH INTERCHANGE	✓	
PRESCRIPTION CONTAINS ALL REQUIRED INFORMATION	✓	
ORALLY COMMUNICATED PRESCRIPTIONS ARE IMMEDIATELY DOCUMENTED	✓	
COMMENTS: <i>Regulations Reviewed</i>		

OUTDATED ITEMS/RETURN TO STOCK	YES	NO
QUARANTINE AREA FOR CONTROLLED SUBSTANCE RECALLS OR EXPIRED PRODUCT SEGREGATED FROM CURRENT INVENTORY	✓	
COMMENTS: <i>Regulations Reviewed</i>		

CONTROLLED SUBSTANCE RECORDS/EDT 21 CFR PART 1300 - 1308 and 247 CMR 5.00	YES	NO
PRESCRIPTION RECORDS ARE ON SITE AND READILY RETRIEVABLE FOR 2 YEARS	✓	

CONTROLLED SUBSTANCE RECORDS/EDT 21 CFR PART 1300 – 1308 and 247 CMR 5.00 (continued)	YES	NO
THE LAST BIENNIAL INVENTORY COMPLETED <u>07/23</u> AND SHOWS BEFORE OPENING OR AFTER CLOSING	<input checked="" type="checkbox"/>	<input type="checkbox"/>
POWER OF ATTORNEY GRANTED TO PERSONS SIGNING DEA FORM 222 AND READILY AVAILABLE	<input checked="" type="checkbox"/>	<input type="checkbox"/>
POWER OF ATTORNEY FORM FOR DEA FORM 222 GRANTED TO: <u>none</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
COMPLETE RETURN AND DESTRUCTION RECORDS OF CONTROLLED SUBSTANCES READILY AVAILABLE	<input checked="" type="checkbox"/>	<input type="checkbox"/>
EMERGENCY C-II PRESCRIPTION RECORDS ARE COMPLETE AND PROPERLY FILED	<input checked="" type="checkbox"/>	<input type="checkbox"/>
SCHEDULE II PRESCRIPTION DATA TRANSMITTED BY COMPUTER ON TIME (EDT)	<input checked="" type="checkbox"/>	<input type="checkbox"/>
CENTRAL RECORD KEEPING AUTHORITY FILED WITH DEA	<input checked="" type="checkbox"/>	<input type="checkbox"/>
DEA ORDER FORMS FILLED OUT COMPLETELY, INCLUDING DATE AND QUANTITY RECEIVED	<input checked="" type="checkbox"/>	<input type="checkbox"/>
CII ORDER FORMS RECONCILED SATISFACTORILY	<input checked="" type="checkbox"/>	<input type="checkbox"/>
CII-V INVOICES RECONCILED SATISFACTORILY	<input checked="" type="checkbox"/>	<input type="checkbox"/>
DAILY REPORTS ARE AVAILABLE, VERIFIED, AND SIGNED BY ALL PHARMACISTS INVOLVED	<input checked="" type="checkbox"/>	<input type="checkbox"/>
CII PERPETUAL INVENTORY RECONCILED WITHIN 10 DAYS	<input checked="" type="checkbox"/>	<input type="checkbox"/>
COMMENTS <i>Regulations Reviewed</i>		

TRANSFER OF PRESCRIPTIONS - 247 CMR 9.02	YES	NO
CORRECT TRANSFER RECORDS ARE MAINTAINED AND READILY AVAILABLE	<input checked="" type="checkbox"/>	<input type="checkbox"/>
DAILY REPORTS ARE AVAILABLE, VERIFIED AND SIGNED BY ALL PHARMACISTS INVOLVED	<input checked="" type="checkbox"/>	<input type="checkbox"/>
PATIENT PROFILES ARE MAINTAINED	<input checked="" type="checkbox"/>	<input type="checkbox"/>
COMMENTS <i>Regulations Reviewed</i>		

EQUIPMENT and REFERENCE SOURCES - 247 CMR 6.01	YES	NO
COMPUTER SOFTWARE NAME: <u>PK</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
TORSION BALANCE AND WEIGHTS SEALED DATE <u>11/08</u>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
COMPOUNDING LOG MAINTAINED	<input checked="" type="checkbox"/>	<input type="checkbox"/>
APPROPRIATELY SIZED SAFETY CONTAINERS AVAILABLE AND USED ROUTINELY (16 CFR 1700)	<input checked="" type="checkbox"/>	<input type="checkbox"/>
CURRENT COPY OR E-VERSION OF APPROPRIATE COMPENDIA REFERENCE AVAILABLE	<input checked="" type="checkbox"/>	<input type="checkbox"/>
CURRENT COPY OR E-VERSION OF MA BOARD OF PHARMACY REGULATIONS AVAILABLE	<input checked="" type="checkbox"/>	<input type="checkbox"/>
CURRENT COPY OR E-VERSION OF MA LIST OF INTERCHANGEABLE DRUGS AVAILABLE	<input checked="" type="checkbox"/>	<input type="checkbox"/>
COMMENTS <i>Regulations Reviewed</i>		

CONTINUOUS QUALITY IMPROVEMENT (CQI) PROGRAM QUALITY RELATED EVENTS (QRE) - 247 CMR 15.00	YES	NO
CURRENT COPY OR E-VERSION OF CQI PROGRAM AVAILABLE	✓	
QRE RECORDS (2 YEARS) ARE MAINTAINED IN AN ORDERLY MANNER AND FILED BY DATE	✓	
PHARMACY PROVIDES PERSONNEL WITH ONGOING CQI EDUCATION AT LEAST ANNUALLY	✓	
POLICY AND PROCEDURES ON SITE RELATED TO THE HANDLING OF MEDICATION ERRORS	✓	
COMMENTS <i>Regulations Reviewed</i>		

PATIENT COUNSELING - 247 CMR 6.01 and 9.07; M.G.L. c. 94C, § 21A	YES	NO
PATIENT COUNSELING SIGNS (11" x 14") POSTED (INCLUDING DRIVE-THRU)	✓	
ADEQUATE OFFER TO COUNSEL MADE AND DOCUMENTED	✓	
DESIGNATED CONFIDENTIAL PATIENT CONSULTATION AREA	✓	
COUNSELING AREA ASSURES PRIVACY AND CONFIDENTIALITY	✓	
PROSPECTIVE DUR ON NEW PRESCRIPTIONS CONDUCTED	✓	
COMMENTS <i>Regulations Reviewed</i>		

SANITATION - 247 CMR 6.02 and 9.01	YES	NO
PHARMACY (INCLUDING SINK, REFRIGERATOR, COUNTING TRAYS, AND AUTOMATED DISPENSING MACHINES) KEPT CLEAN AND ORGANIZED	✓	
REFRIGERATOR MAINTAINED WITHING RANGE COMPLIANT WITH STORAGE OF DRUGS REQUIRING REFRIDGERATION TEMP. <i>38°</i>	✓	
ROOM TEMPERATURE IS 59 - 77 DEGREES F.	✓	
PRESCRIPTION COUNTER IS USED ONLY FOR PREPARING PRESCRIPTIONS	✓	
PRESCRIPTION DEPARTMENT HAS SPACE ADEQUATE FOR THE SIZE AND SCOPE OF PHARMACEUTICAL SERVICES PROVIDED BY THE PHARMACY	✓	
SUFFICIENT EQUIPMENT TO COMPOUND AND DISPENSE PRESCRIPTIONS	✓	
SINK HAS HOT AND COLD RUNNING WATER	✓	
COMMENTS <i>Regulations Reviewed</i>		

CENTRAL INTRAVENOUS ADMIXTURE SERVICE (CIVAS) 247 CMR 6.01(5)(c)	YES	NO
CLEAN ROOM - MINIMUM OF 72 SQUARE FEET	✓	
CLEAN ROOM ADJACENT TO PRESCRIPTION DEPARTMENT	✓	
HOODS: HORIZONTAL VERTICAL	✓	
CIVAS APPROVAL LETTER FROM BOARD MAINTAINED ON PREMISES	✓	<i>Pending</i>

CENTRAL INTRAVENOUS ADMIXTURE SERVICE (CIVAS) 247 CMR 6.01(5)(c) continued	YES	NO
WRITTEN QUALITY ASSURANCE GUIDELINES MAINTAINED ON PREMISES	✓	
TRAINING IN STERILE PROCEDURE AVAILABLE AND CONDUCTED	✓	
ADEQUATE REFERENCE STANDARDS	✓	
ANNUAL CERTIFICATION OF LAMINAR HOOD AND CLEAN ROOM CONDUCTED	✓	
COMMENTS: <i>Regulations Reviewed Certifications Enclosed</i>		

TECHNICIANS - 247 CMR 8.00	YES	NO
PHARMACY TECHNICIANS OPERATE WITHIN THE SCOPE OF LAW AND REGULATIONS	✓	
TECHNICIANS WEAR NAME TAGS EASILY READABLE WITH TITLE AND NAME	✓	
TECHNICIANS FOLLOW DUTIES AS SPECIFIED IN WRITTEN POLICIES AND PROCEDURES	✓	
TECHNICIANS ARE SUPERVISED BY A PHARMACIST	✓	
COMMENTS: <i>Regulations Reviewed</i>		

VACCINATION/CPR - 105 CMR 700.004	YES	NO
PHARMACIST ADMINISTERING VACCINES TO PERSONS 18 YEARS OF AGE OR OLDER		
CURRENT CPR CARD		
ADMINISTRATION IS CONDUCTED PURSUANT TO THE ORDER OF A PRACTITIONER		
DOCUMENTATION OF ACCREDITED TRAINING		
COMMENTS:		

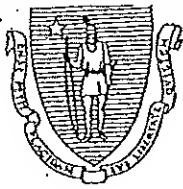
MANAGER OF RECORD (MOR) - 247 CMR 6.07	YES	NO
MOR CAN DEMONSTRATE IMPLEMENTATION OF A CQI PROGRAM	✓	
MOR HAS COPIES OF CONFIDENTIALITY STATEMENTS FROM EACH EMPLOYEE	✓	
MOR IS RESPONSIBLE FOR ESTABLISHING AND MONITORING POLICIES AND PROCEDURES:	✓	
(a) STAFF TRAINING ONGOING	✓	
(b) TECHNICIAN MANUAL ON PREMISES	✓	
(c) RATIO PHARMACIST TO SUPPORT PERSONNEL _____	✓	
NO. ON STAFF:	✓	
PHARMACISTS _____ PHARMACY INTERNS _____	✓	
REGISTERED TECHS _____ CERTIFIED TECHS _____ TECHS IN TRAINING _____	✓	
COMMENTS: <i>Regulations Reviewed</i>		

WHOLESALE DISTRIBUTOR INFORMATION	
NAME(S) OF SUPPLIERS: <i>Direct Manufacturers</i>	

GENERAL	YES	NO
PHARMACY GRANTED ANY WAIVERS BY THE BOARD OR DEA TO ANY LAWS OR RULES	<input checked="" type="checkbox"/>	<input type="checkbox"/>
PHARMACY SHARES A REAL-TIME COMMON DATABASE WITH OTHER PHARMACIES	<input checked="" type="checkbox"/>	<input type="checkbox"/>
PHARMACY UTILIZE THE SERVICES OF A CENTRAL FILL PHARMACY	<input checked="" type="checkbox"/>	<input type="checkbox"/>
VERIFYING PHARMACIST(S) IS DOCUMENTED	<input checked="" type="checkbox"/>	<input type="checkbox"/>
PHARMACY PERSONNEL WEAR APPROPRIATE NAME TAGS	<input checked="" type="checkbox"/>	<input type="checkbox"/>
PROCEDURE TO ENSURE ALL WHO WORK IN THE PHARMACY ARE APPROPRIATELY AND CURRENTLY REGISTERED OR LICENSED AND TRAINED TO PERFORM THEIR DUTIES	<input checked="" type="checkbox"/>	<input type="checkbox"/>
SIGN(S) POSTED REGARDING PHARMACY HOURS OF OPERATION	<input checked="" type="checkbox"/>	<input type="checkbox"/>
COMMENTS: <i>Regulations Reviewed</i>		

I have participated in an inspection and have reviewed the Inspection Report with the Investigator.

Print Name: *Steven Perry* Signature: *Steven Perry*
 Title: *Pharmacy Manager of Records* License No. *17303*
 Investigator: *J. Green* Date: *11/19/08*



Executive Office of Health and Human Services
Department of Public Health
Division of Health Professions Licensure
239 Causeway Street, Suite 200
Boston, MA 02114

J-752

Office of Public Protection
(617) 973-0865 Fax (617) 973-0985 TTY (617)-973-0895

INSPECTION REPORT

Date of Inspection 1/7/11 Reg. No. Pending Expiration Date

Purpose of Inspection New Location Relocation ☒ Compliance

Docket No. OR Staff Assignment No. ISP 592

Corporation Name Ameridose

Pharmacy DBA Name

Store No.

Address 201 Flanders Rd Westborough MA 01581

Telephone No. 508-656-2653 Fax No. 508-775-0556

Manager of Record Sophia Paredis Reg. No. 20017

Pharmacy DEA Registration No. and Expiration Date Pending

Pharmacy Hours Daily 7 - 7 Saturday Sunday

Practice Setting Community Chain With Drive-thru Window ☒
Community Independent Specialty Long Term Care

Daily Pharmacy Volume Less than 100 100 to 500 Above 500

Staff Pharmacists (Names and Registration Numbers)

Enclosed

Pharmacy Interns (Names and Registration Numbers)

Pharmacy Technicians (Names, Registration Numbers and Certification Status)

Other Pharmacy Support Staff and Trainees (Names and positions)

SECURITY - 247 CMR 6.02 and CFR 1301.75(b)	YES	NO
ADEQUATE SECURITY SYSTEM	✓	
EVIDENCE OF SECURITY CAMERAS	✓	
SECURITY BARRIER SEPARATES PHARMACY DEPARTMENT	N/A	
PROCEDURE FOR ABSENCE OF PHARMACIST	✓	
CONTROLLED SUBSTANCES ARE LOCKED IN A SECURE CABINET	✓	
CONTROLLED SUBSTANCES ARE DISPERSED THROUGHOUT GENERAL INVENTORY	✓	
LOSS OR THEFT OF CONTROLLED SUBSTANCES (DEA FORM 106) REPORTED TO THE BOARD	✓	
SECURITY/ACCESS TO PHARMACY RESTRICTED TO AUTHORIZED PERSONNEL	✓	
COMMENTS:		

LICENSURE/REGISTRATION STATUS OF PHARMACY STAFF	YES	NO
COPIES OF PHARMACIST LICENSES ARE POSTED AND CURRENT	✓	
COPIES OF TECHNICIAN REGISTRATIONS ARE CURRENT AND AVAILABLE	✓	
PROCEDURES IN PLACE TO MAINTAIN PATIENT CONFIDENTIALITY WITH REGARD TO DISCARDED PRESCRIPTION INFORMATION (e.g. SHREDDER)	✓	
COMMENTS: <i>Enclosed</i>		

STANDARDS FOR PRESCRIPTION LABELING AND FORMAT M.G.L. c. 94C, § 21 and CMR 721.000	YES	NO
PHARMACIST INITIALS ON LABEL AND SERIAL NO. OF Rx		✓
"BEYOND USE" DATE IS SHOWN ON LABEL		✓
INVENTORY LABELED WITH BRAND, OR GENERIC NAME AND MANUFACTURER, STRENGTH, LOT NUMBER, EXPIRATION DATE, OR INTERNAL CONTROL NUMBER WHICH REFERENCES MANUFACTURER AND LOT NUMBER USED	✓	
LABEL COMPLIANT WITH INTERCHANGE	✓	
PRESCRIPTION CONTAINS ALL REQUIRED INFORMATION	✓	
ORALLY COMMUNICATED PRESCRIPTIONS ARE IMMEDIATELY DOCUMENTED		N/A
COMMENTS: <i>Copy enclosed</i>		

OUTDATED ITEMS/RETURN TO STOCK	YES	NO
QUARANTINE AREA FOR CONTROLLED SUBSTANCE RECALLS OR EXPIRED PRODUCT SEGREGATED FROM CURRENT INVENTORY	✓	
COMMENTS: <i>Area identified</i>		

CONTROLLED SUBSTANCE RECORDS/EDT 21 CFR PART 1300 - 1308 and 247 CMR 5.00	YES	NO
PRESCRIPTION RECORDS ARE ON SITE AND READILY RETRIEVABLE FOR 2 YEARS	✓	

CONTROLLED SUBSTANCES 21 CFR PART 1300 - 1308 and 247 CMR 5.00 (continued)

THE LAST BIENNIAL INVENTORY COMPLETED opening AND SHOWS BEFORE OPENING OR AFTER CLOSING

POWER OF ATTORNEY GRANTED TO PERSONS SIGNING DEA FORM 222 AND READILY AVAILABLE

POWER OF ATTORNEY FORM FOR DEA FORM 222 GRANTED TO: MDR

COMPLETE RETURN AND DESTRUCTION RECORDS OF CONTROLLED SUBSTANCES READILY AVAILABLE

EMERGENCY C-II PRESCRIPTION RECORDS ARE COMPLETE AND PROPERLY FILED

SCHEDULE II PRESCRIPTION DATA TRANSMITTED BY COMPUTER ON TIME (EDT)

CENTRAL RECORD KEEPING AUTHORITY FILED WITH DEA

DEA ORDER FORMS FILLED OUT COMPLETELY, INCLUDING DATE AND QUANTITY RECEIVED

CII ORDER FORMS RECONCILED SATISFACTORILY

CIII-V INVOICES RECONCILED SATISFACTORILY

DAILY REPORTS ARE AVAILABLE, VERIFIED, AND SIGNED BY ALL PHARMACISTS INVOLVED

CII PERPETUAL INVENTORY RECONCILED WITHIN 10 DAYS

COMMENTS

TRANSFER OF PRESCRIPTIONS - 247 CMR 9.02

CORRECT TRANSFER RECORDS ARE MAINTAINED AND READILY AVAILABLE

DAILY REPORTS ARE AVAILABLE, VERIFIED AND SIGNED BY ALL PHARMACISTS INVOLVED

PATIENT PROFILES ARE MAINTAINED

COMMENTS

EQUIPMENT and REFERENCE SOURCES - 247 CMR 6.01

COMPUTER SOFTWARE NAME: Extra-net

TORSION BALANCE AND WEIGHTS SEALED DATE

COMPOUNDING LOG MAINTAINED

APPROPRIATELY SIZED SAFETY CONTAINERS AVAILABLE AND USED ROUTINELY (16 CFR 1700)

CURRENT COPY OR E-VERSION OF APPROPRIATE COMPENDIA REFERENCE AVAILABLE

CURRENT COPY OR E-VERSION OF MA BOARD OF PHARMACY REGULATIONS AVAILABLE

CURRENT COPY OR E-VERSION OF MA LIST OF INTERCHANGEABLE DRUGS AVAILABLE

COMMENTS

Enclosed

CONTINUOUS QUALITY IMPROVEMENT QUALITY RELATED EVENTS (QRE) - 247 CMR 15.00

CURRENT COPY OR E-VERSION OF CQI PROGRAM AVAILABLE	✓	
QRE RECORDS (2 YEARS) ARE MAINTAINED IN AN ORDERLY MANNER AND FILED BY DATE	✓	
PHARMACY PROVIDES PERSONNEL WITH ONGOING CQI EDUCATION AT LEAST ANNUALLY	✓	
POLICY AND PROCEDURES ON SITE RELATED TO THE HANDLING OF MEDICATION ERRORS	✓	
COMMENTS		

PATIENT COUNSELING

247 CMR 6.01 and 9.07; M.G.L. c. 94C, § 21A

PATIENT COUNSELING SIGNS (11" x 14") POSTED (INCLUDING DRIVE THRU)

ADEQUATE OFFER TO COUNSEL MADE AND DOCUMENTED

DESIGNATED CONFIDENTIAL PATIENT CONSULTATION AREA

COUNSELING AREA ASSURES PRIVACY AND CONFIDENTIALITY

PROSPECTIVE DUR ON NEW PRESCRIPTIONS CONDUCTED

COMMENTS

YES NO

✓
✓
✓
✓

SANITATION - 247 CMR 6.02 and 9.01

PHARMACY (INCLUDING SINK, REFRIGERATOR, COUNTING TRAYS, AND AUTOMATED DISPENSING MACHINES) KEPT CLEAN AND ORGANIZED

REFRIGERATOR MAINTAINED WITHIN RANGE COMPLIANT WITH STORAGE OF DRUGS REQUIRING REFRIDGERATION TEMP. 38°

ROOM TEMPERATURE IS 59 - 77 DEGREES F. 62°

PRESCRIPTION COUNTER IS USED ONLY FOR PREPARING PRESCRIPTIONS

PRESCRIPTION DEPARTMENT HAS SPACE ADEQUATE FOR THE SIZE AND SCOPE OF PHARMACEUTICAL SERVICES PROVIDED BY THE PHARMACY

SUFFICIENT EQUIPMENT TO COMPOUND AND DISPENSE PRESCRIPTIONS

SINK HAS HOT AND COLD RUNNING WATER

COMMENTS

28 sec air exchange

YES NO

✓
✓
✓
✓
✓
✓

CENTRAL INTRAVENOUS ADMIXTURE SERVICE (CIVAS) 247 CMR 6.01(5)(c)

CLEAN ROOM - MINIMUM OF 72 SQUARE FEET

CLEAN ROOM ADJACENT TO PRESCRIPTION DEPARTMENT

HOODS: HORIZONTAL
VERTICAL

CIVAS APPROVAL LETTER FROM BOARD MAINTAINED ON PREMISES

YES NO

✓
✓
✓
✓

Results enclosed in SPA ISP 592

CENTRAL INTRAVENOUS

247 CMR 6.01(5)(c) continued

WRITTEN QUALITY ASSURANCE GUIDELINES MAINTAINED ON PREMISES ✓
 TRAINING IN STERILE PROCEDURE AVAILABLE AND CONDUCTED ✓
 ADEQUATE REFERENCE STANDARDS ✓
 ANNUAL CERTIFICATION OF LAMINAR HOOD AND CLEAN ROOM CONDUCTED ✓

COMMENTS:

Enclosed

TECHNICIANS - 247 CMR 8.00

PHARMACY TECHNICIANS OPERATE WITHIN THE SCOPE OF LAW AND REGULATIONS ✓
 TECHNICIANS WEAR NAME TAGS EASILY READABLE WITH TITLE AND NAME *N/A*
 TECHNICIANS FOLLOW DUTIES AS SPECIFIED IN WRITTEN POLICIES AND PROCEDURES ✓
 TECHNICIANS ARE SUPERVISED BY A PHARMACIST ✓
 COMMENTS:

YES

NO

VACCINATION/CPR - 105 CMR 700.004

PHARMACIST ADMINISTERING VACCINES TO PERSONS 18 YEARS OF AGE OR OLDER ✓
 CURRENT CPR CARD *N/A*
 ADMINISTRATION IS CONDUCTED PURSUANT TO THE ORDER OF A PRACTITIONER ✓
 DOCUMENTATION OF ACCREDITED TRAINING ✓
 COMMENTS:

YES

NO

MANAGER OF RECORD (MOR) - 247 CMR 6.07

MOR CAN DEMONSTRATE IMPLEMENTATION OF A CQI PROGRAM ✓
 MOR HAS COPIES OF CONFIDENTIALITY STATEMENTS FROM EACH EMPLOYEE ✓
 MOR IS RESPONSIBLE FOR ESTABLISHING AND MONITORING POLICIES AND PROCEDURES:
 (a) STAFF TRAINING ONGOING ✓
 (b) TECHNICIAN MANUAL ON PREMISES ✓
 (c) RATIO PHARMACIST TO SUPPORT PERSONNEL *1:3* ✓
 NO. ON STAFF:
 PHARMACISTS *1* PHARMACY INTERNS *0*
 REGISTERED TECHS *2* CERTIFIED TECHS *1* TECHS IN TRAINING *0*

YES

NO

COMMENTS:

1:3

Employee roster enclosed

NAME(S) OF SUPPLIERS:

McKesson

GENERAL		YES	NO
PHARMACY GRANTED ANY WAIVERS BY THE BOARD OR DEA TO ANY LAWS OR RULES		✓	✓
PHARMACY SHARES A REAL-TIME COMMON DATABASE WITH OTHER PHARMACIES			✓
PHARMACY UTILIZE THE SERVICES OF A CENTRAL FILL PHARMACY		✓	✓
VERIFYING PHARMACIST(S) IS DOCUMENTED		N/A	
PHARMACY PERSONNEL WEAR APPROPRIATE NAME TAGS		✓	
PROCEDURE TO ENSURE ALL WHO WORK IN THE PHARMACY ARE APPROPRIATELY AND CURRENTLY REGISTERED OR LICENSED AND TRAINED TO PERFORM THEIR DUTIES		✓	
SIGN(S) POSTED REGARDING PHARMACY HOURS OF OPERATION			
COMMENTS:			

I have participated in an inspection and have reviewed the Inspection Report with the Investigator.

Print Name SOPHIA PASOLOS Signature [Signature]
 Title VP Reg Affairs + Compliance License No. 20217
 Investigator [Signature] Date 1/7/11

FDA Inspection Report for Ameridose (Sept. 2008)

Establishment Inspection Report
Ameridose, LLC
Framingham, MA 01702-6211

FEI: 3005881167
EI Start: 09/17/2008
EI End: 09/18/2008

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SUMMARY

This FY 2008 limited inspection of Ameridose, LLC was conducted in follow up to the firm's previous drug inspection and recent product recall. This inspection was conducted in accordance with Drug Manufacturing Inspections Compliance Program 7356.002 and FACTS 970608.

Ameridose was last inspected July 21 through August 6, 2008. A Form FDA 483 Inspectional Observations was issued for 1) testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release; 2) written procedures are lacking which describe in sufficient detail the identification, sampling, testing, approval, and rejection of components; 3) master production and control records are deficient in that they do not include a statement of theoretical yield and minimum, maximum, and yield percentages; 4) hatch production and control records do not include results of the inspection of the packaging and labeling area before and after use for each hatch of drug product produced; 5) batch production and control records are deficient in that they do not include a statement of the actual yield and percentage of theoretical yield; and 6) written production and process control procedures are not followed in the execution of production and process control functions. Mr. Conigliaro stated a written response to the Form FDA 483 was submitted on or about August 22nd.

Establishment Inspection Report
Ameridose, LLC
Framingham, MA 01702-6211

FBI: 3005881167
EI Start: 09/17/2008
EI End: 09/18/2008

As part of the previous inspection FDA samples 366491 – Fentanyl (as Citrate) and 366492 – Oxytocin were collected and tested for sterility, potency and identity. Based on the results of sample 366491, on September 12th, the firm initiated a voluntary product recall for the potential product “potency may be higher than the labeled value”. Sample 366492 results are pending.

This inspection covered review of manufacturing worksheets, labeling, invoices and shipping records specific to samples 366491 and 366492 as well as follow up discussion specific to questions addressed during the previous inspection. A Form FDA 463a Affidavit was signed by Gregory A. Conigliaro, General Manager/Vice President. A Form FDA 483 was not issued and additional samples were not collected.

ADMINISTRATIVE DATA

Post inspectional correspondence should be addressed to Mr. Gregory A. Conigliaro, General Manager/Vice President at the referenced mailing address.

Inspected Firm:	Ameridose, LLC
Corporate Location:	50 Fountain Street Framingham, MA 01702-6211
Manufacture Location:	695 Waverly Street Framingham, MA Framingham, MA 01702-6211
Phone:	508-656-2653
FAX:	508-820-0644
Mailing Address:	50 Fountain Street Framingham, MA 01702-6211
Website:	www.ameridose.com
Dates of Inspection:	9/17/2008, 9/18/2008
Days in Facility:	2
Participants:	Michelle M. Noe, Investigator

On September 15th, FDA credentials were displayed and a completed Form FDA 482 Notice of Inspection was issued by FDA Investigator Madigan to Mr. Gregory A. Conigliaro. (Attachment 1)

This inspection was preannounced to Mr. Gregory A. Conigliaro, General Manager/Vice President on September 16th for he called the New England District Office questioning the whereabouts of Investigator Madigan. She had planned to return to the firm on September 16th; however, she was deployed for a U.S. Public Health Service mission.

Establishment Inspection Report
Ameridose, LLC
Framingham, MA 01702-6211

FEI: 3005881167
EI Start: 09/17/2008
EI End: 09/18/2008

On September 17th, FDA credentials were displayed and a completed Form FDA 482 Notice of Inspection was issued by me to Mr. Gregory A. Conigliaro. (*Attachment 2*)

On September 18th, Mr. Gregory A. Conigliaro, General Manager/Vice President signed a Form FDA 463a Affidavit. (*Attachment 3*)

HISTORY

Ameridose, LLC is a private domestic limited liability company which organized on February 8, 2006 in the State of Massachusetts. Mr. Gregory A. Conigliaro and Mr. Barry J. Cadden are designated as Managers of the business. On July 13, 2006, the company opened operations at its present locations, 50 Fountain Street Framingham, MA and 695 Waverly Street Framingham, MA. Mr. Conigliaro stated the company has no subsidiaries or related businesses and no other locations.

Previous Inspection

Ameridose was last inspected July 21st through August 6, 2008. A Form FDA 483 Inspectional Observations was issued for 1) testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release; 2) written procedures are lacking which describe in sufficient detail the identification, sampling, testing, approval, and rejection of components; 3) master production and control records are deficient in that they do not include a statement of theoretical yield and minimum, maximum, and yield percentages; 4) batch production and control records do not include results of the inspection of the packaging and labeling area before and after use for each batch of drug product produced; 5) batch production and control records are deficient in that they do not include a statement of the actual yield and percentage of theoretical yield; and 6) written production and process control procedures are not followed in the execution of production and process control functions. Mr. Conigliaro stated a written response to the Form FDA 483 was submitted on or about August 22nd.

As part of the previous inspection, FDA sample 366491 – Fentanyl (as Citrate) and 366492 – Oxytocin was collected and tested for sterility, potency and identity. Based on the results of sample 366491, on September 12th, the firm initiated a voluntary product recall due to the potential that the product "potency may be higher than the labeled value". Sample 366492 results are pending.

INTERSTATE COMMERCE

Based on the previous establishment report, Ameridose ships 75% of its finished product outside the State of Massachusetts. According to the company website, Ameridose services all 50 states.

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Hospitals are the firm's primary customers. Purchase orders are received from a hospital pharmacist and/or purchase/buyer via facsimile or internet at <http://www.ameridose.com/Ameridose-Online-Ordering.html>. Documentation of interstate shipping records for samples 366491 and 366492 were collected. Finished product is shipped directly from Ameridose to its customers via FEDEX. Mr. Conigliaro stated FEDEX is considered the firm's primary shipper and performs an estimated 95% of its deliveries.

JURISDICTION

Ameridose is a unit dose repackaging and sterile admixing services company. Based on the previous establishment report, Ameridose markets and distributes over 600 products including: seven (7) antibiotic classes; fifteen (15) Class II; one (1) Class III; two (2) Class IV; and many Class VI products. A product list was collected during the previous inspection. According to the company website, Ameridose offers the following products for sale to customers nationwide:

Sterile Admixing Services

Antibiotic Admixtures	Electrolyte Admixtures
PCA Admixtures	Operating Room Syringes
Epidural Admixtures	Sterile Repackaged Syringes
Labor & Delivery Admixtures	Miscellaneous Admixtures

Oral Syringe Repackaging Services

Schedule II Narcotics	Schedule IV Controlled Substances
Hydromorphone	Chloral Hydrate
Meperidine	Diazepam
Methadone	Lorazepam
Morphine	Midazolam
Oxycodone	Phenobarbital
Schedule III Combination Controlled Substances	Schedule V Combination Controlled Substances
Hydrocodone Bitartrate / Acetaminophen	Codeine / Guaifenesin
Hydrocodone Bitartrate / Ibuprofen	Codeine / Guaifenesin / Phenylephrine
Hydrocodone / Guaifenesin	Schedule VI (Legend Drugs) & OTC
Hydrocodone / Guaifenesin / Phenylephrine	Vancomycin
Tylenol with Codeine	Others upon Request

Mr. Conigliaro reported 99% of the firm's business is not patient specific and the remaining 1% is patient specific (i.e. dialysis patients). Mr. Conigliaro stated that, except for dialysis patient purchase orders, Ameridose does not receive patient names on customer orders, only the total quantity requested. Mr. Conigliaro noted Ameridose does not service home delivery. Ameridose is responsible for the labeling of finished product. Examples of product labels for Fentanyl and

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Oxytocin were collected. Refer to the section of this report entitled, "Manufacturing/Design Operations".

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

A photocopy of the Ameridose organizational chart was collected and attached as *Exhibit 1*.

Gregory A. Conigliaro
Vice President/General Manager

Mr. Conigliaro identified himself as the most responsible individual. He stated he is Vice President/General Manager and has been since the company was founded in February 2006, noting there is no designated President. He explained he has the authority to sign checks, take loans and hire personnel. He stated he has a background in engineering. Mr. Conigliaro explained he does not report to a specific individual but is accountable to the Board of Members. There are four individuals which make up the Board of Members. Mr. Barry Cadden is designated as one of the four Members. Mr. Conigliaro noted the Board of Members are not involved in the day-to-day activities of the business; however, Mr. Cadden has the authority to act as his designee (i.e. sign checks). Mr. Conigliaro chose not to disclose the other Members. Note: Mr. Cadden is Mr. Conigliaro's brother-in-law. He is President/Director of New England Compounding Pharmacy, Inc. located at 697 Waverly Street Framingham, MA. Mr. Conigliaro stated Mr. Cadden owns the patient specific compounding pharmacy and that Mr. Cadden's "company is not an FDA facility, it is purely a pharmacy located in the State of Massachusetts."

Mr. Conigliaro confirmed that he is most responsible for all operations of Ameridose and as such, has full knowledge of the day-to-day operations including regulatory, manufacturing, human resources, and financials. He has knowledge of, and can identify, records associated with the receipt, storage, manufacture, label, and shipment of inventories by the firm. (*Attachment 3*) Mr. Conigliaro has several direct reports at the management level, i.e. Ms. Sophia Pasedis, Vice President Regulatory Affairs, PIC, responsible for pharmacy oversight (18 pharmacists) and FDA regulations. Mr. Conigliaro stated that Ameridose is "an FDA facility, naturally."

Melanie Cerullo
Director of Quality

Ms. Cerullo reported she is responsible for the firm's overall quality system including, documentation, training, change control, deviations, complaints and routine quality review. Ms. Cerullo stated she is responsible for release of in-process and finished product. Ms. Cerullo has been employed by Ameridose since October 1, 2007 and reports to Mr. Conigliaro.

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MANUFACTURING/DESIGN OPERATIONS

ORDER RECEIPT / PROCESSING

Mr. Conigliaro stated all purchase orders are received from a hospital pharmacist and/or purchase/buyer via facsimile or internet at <http://www.ameridose.com/Ameridose-Online-Ordering.html>. He noted Ameridose does not service home delivery and does not work with a wholesale supply chain. SOPs No. 2.040 version 1.0 entitled, "Order Process" and 2.0 (draft) entitled, "Order Processing and Generation of Formulary Worksheet" were reviewed.

Mr. Conigliaro reported 99% of the firm's business is not patient specific and the remaining 1% is patient specific (i.e. dialysis patients). He stated that, except for dialysis patient purchase orders, Ameridose does not receive patient names on customer orders, only the total quantity requested. To fill orders product is either pulled from the firm's existing inventory or a new lot is manufactured.

Ms. Cerullo stated Ameridose uses PK Software, generic pharmacy software, which randomly assigns a lot number (in-process and finished product) and generates an order label. This order label is not used on the product. Refer to *Exhibit 7, pages 4, 6, 8, 10, 12 & Exhibit 12, pages 2, 4, 7, 9, 18, 12, 15, 21, 24, 26, 28*. It is only affixed to the purchase order form. This label includes an Rx number. This Rx number is not used by Ameridose, for the firm relies on the customer order number and lot number to track product. Mr. Conigliaro stated Ameridose uses Quick Books to generate its packing slips and invoices. Finished product is shipped directly from Ameridose to its customers via FEDEX. FEDEX labels are affixed to the invoices. Refer to *Exhibit 7, pages 5, 7, 9, 11, 13 & Exhibit 12, pages 3, 5, 8, 11, 13, 16, 19, 22, 25, 27, 29*. FEDEX is considered the firm's primary shipper and performs an estimated 95% of its deliveries.

FENTANYL CITRATE 0.9% NACL 10mcg/mL - Lot 07302008@4

RAW MATERIAL

On or about July 1, 2008 Ameridose received a shipment consisting of two (25gm) units of Fentanyl Citrate Powder-USP (non-sterile active) - Lot 66559A from Medisca Inc. Plattsburgh, NY via FEDEX (no tracking number available). A photocopy of raw material shipment/receipt and certificate of analysis was collected and attached as *Exhibit 2*.

Ms. Cerullo stated the firm does not perform identity testing on incoming raw material for it relies on the certificate of analysis. She confirmed that raw material testing of incoming product is not included in the firm's current SOPs. Ms. Cerullo did note that some raw materials have been identity tested but it is not the firm's normal practice to do so and that these raw materials were tested solely for a specific reason, i.e. development. She explained that Ms. Pasedis was the best person to ask regarding this question; however, she was not available.

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CONCENTRATE

A portion of Lot 66559A was used on July 2, 2008 to manufacture five (20mL) syringes and thirty (50mL) syringes of Fentanyl Concentrate in H₂O 10mg/mL, Lot 07012008@96. A photocopy of the manufacture worksheet was collected and attached as Exhibit 3. The firm does not perform identity testing on the concentrate.

STOCK SOLUTION

A portion of Lot 07012008@96 was used on July 9, 2008 and July 15, 2008 to manufacture Fentanyl (as Citrate) in SWFI 50mcg/mL 4000mL Stock Solution Lot 07082008@109 and Lot 07142008@109, respectively.

Samples of Fentanyl Stock Solution (1 syringe) were sent to DYNALABS to test potency/purity, endotoxin and sterility. Stock Solution were held in quarantine until receipt of results (CoA dated July 28, 2008 and July 30, 2008), and subsequently released by Director of Quality and/or Director of Pharmacy and/or Narcotics Pharmacist.

A photocopy of the manufacture worksheets and certificate of analyses/testing was collected and attached as Exhibit 4 & 5.

FINISHED PRODUCT / LABELING

A portion of Lot 07082008@109 and Lot 07142008@109 was used on or about August 1, 2008 to manufacture 200 finished product units: Fentanyl Citrate in 0.9% NACL 10mg/mL 100mL Injectable bag, Lot 07302008@4.

A sample of finished product (1 syringe) pulled from multiple finished product injectable bags was sent to DYNALABS to test 14 day sterility. The only test performed on all finished products is sterility. It is the firm's normal practice to release finished product prior to receipt of results. Lot 07302008@4 was released by a Staff Pharmacist prior to receipt of sterility results (CoA dated August 19, 2008), upon final inspection of the lot.

A photocopy of the manufacture worksheets and certificate of analysis/testing was collected and attached as Exhibit 6.

For Fentanyl, Ameridose affixes a white label with black lettering on Hospira injectable bags. The Ameridose label covers the Hospira blue lettering imprinted on the bag, however, a portion of the lettering remains visible which includes but is not limited to, "****Lot xxx Exp xxx 100 mL NDC 0409-7984-37 0.9% SODIUM CHLORIDE Injection, USP****". In addition to the Hospira lettering,

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the finished product is labeled in part, ****Preservative Free 10mcg/mL FENTanyl (as Citrate) in 0.9% Sodium Chloride Total Fentanyl Dose 1,000mcg/100mL Content volume 100mL in 100mL Injectable Bag Exp: xx-xx-xxxx [month/day/year] Lot: xxxxxxxx@xxx Rx Only AMERIDOSE Framingham, MA 01702...CII Store at Room Temperature Single-Dose Bag [BARCODE] NDC: 2420025104****. Each product is placed in an Ameridose over-wrap tamperproof bag. There is no specific labeling on the bag.

A photocopy of an example of the finished product label was collected and attached as *Exhibit 6a*.

FINISHED PRODUCT SHIPMENT

The following customers received shipment of Fentanyl Citrate in 0.9% NACL 10mcg/mL Injectable bag, Lot 07302008@4 via FEDEX. A photocopy of documentation of distributed product including a master customer list for Lot 07302008@4, purchase orders, and invoices with FEDEX tracking numbers were collected and attached as *Exhibit 7*.

Order No.	Customer	Address	Qty Dispensed	Date Dispensed	FEDEX Tracking No.
3574	Advocate Good Samaritan Hospital	Downers Grove, IL	5 bags	7/31/08	9677 5295 4223 9677 5295 4040 9677 5295 4028 9677 5295 4039
3548	Bon Secours Mary Immaculate Hospital	Newport News, VA	10 bags	7/31/08	9677 5295 5539 9677 5295 5528 9677 5295 5517 9677 5295 5506 9677 5295 5491 9677 5295 5480 9677 5295 5470 9677 5295 5469 9677 5295 5458
3710	Craven Regional Medical Center	New Bern, NC	10 bags	8/2/08	9677 5295 5138 9677 5295 5127 9677 5295 5116 9677 5295 5105
3807	Branson Methodist Hospital	Kalamazoo, MI	100 bags	8/4/08	9677 5295 8034 9677 5295 8023 9677 5295 8012 9677 5295 8001 9677 5295 7998 9677 5295 7987

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4086	Caritas Norwood Hospital	Norwood, MA	30 bags	8/6/08	649801860685443 649801860685450
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Oxytocin added to 0.9% NACL 30 units/500mL injectable bag, Lot 08022008@54

RAW MATERIAL

On or about March 14, 2008 my firm received a shipment consisting of one (2.5 million units blk) of Oxytocin, USP (non-sterile active powder) Lot XA0048 from Spectrum Chemical Mfg. Corp. Gardena, CA via FEDEX (no tracking number available). A photocopy of raw material shipment/receipt and certificate of analysis was collected and attached as Exhibit 8.

As previously noted, Ms. Cerullo stated the firm does not perform identity testing on incoming raw material for it relies on the certificate of analysis. She confirmed that raw material testing of incoming product is not included in the firm's current SOPs. Ms. Cerullo did note that some raw materials have been identity tested but it is not the firm's normal practice to do so and that these raw materials were tested solely for a specific reason, i.e. development. She explained that Ms. Pasedis was the best person to ask regarding this question; however, she was not available.

STOCK SOLUTION

A portion of Lot XA0048 was used on July 11, 2008 to manufacture five (4000mL) bags of Oxytocin in SWFI 10 units/mL 4000mL Stock Solution, Lot 07102008@83.

A samples of Oxytocin Stock Solution (1 syringe) was sent to DYNALABS to test potency/purity, endotoxin and sterility. Stock Solution was held in quarantine until receipt of results (CoA dated July 28, 2008), and subsequently released by Director of Quality and/or Director of Pharmacy and/or Narcotics/Vault Pharmacist.

A photocopy of the manufacture worksheet and certificate of analysis/testing was collected and attached as Exhibit 9.

FINISHED PRODUCT / LABELING

A portion of Lot 07102008@83 was used on August 4, 2008 to manufacture 432 finished product units: Oxytocin added to 0.9% NACL 30 units/500mL injectable bag, Lot 08022008@54.

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A sample of finished product (1 syringe) pulled from multiple finished product injectable bags was sent to DYNALABS to test 14 day sterility. The only test performed on all finished products is sterility. It is the firm's normal practice to release finished product prior to receipt of results. Lot 08022008@54 was released by a Staff Pharmacist prior to receipt of sterility results (CoA dated August 20, 2008), upon final inspection of the lot.

A photocopy of the manufacture worksheet and certificate of analysis/testing was collected and attached as *Exhibit 10*.

For Oxytocin, Ameridose affixes a green label with black lettering on Hospira injectable bags. The Ameridose-label covers the Hospira blue lettering imprinted on the bag, however, a portion of the lettering remains visible which includes but is not limited to, "****Lot xxx Exp xxx 500 mL NDC 0409-7983-07 0.9% SODIUM CHLORIDE Injection, USP****". In addition to the Hospira lettering, the finished product is labeled in part, "****OxyTOCIN 30 Units added to 500 mL 0.9% Sodium Chloride Inj. Store at Room Temperature, Protect from Freezing. Exp: xx/xx/xxxx [month/day/year] Rx Only AMERIDOSE Framingham, MA 01702 Single-Dose Bag [Barcode] NDC: 2420020613****". Each product is placed in an Ameridose over-wrap tamperproof bag. There is no specific labeling on the bag.

FINISHED PRODUCT SHIPMENT

The following customers received a shipment of Oxytocin added to 0.9% NACL 30 units/500mL Injectable bags, Lot 08022008@54 via FEDEX. A photocopy of documentation of distributed product including a master customer list for Lot 08022008@54, purchase orders, and invoices with FEDEX tracking numbers were collected and attached as *Exhibit 12*.

Order No.	Customer	Address	Qty Dispensed	Date Dispensed	FEDEX Tracking No.
4191	Riverside Medical Center - Kankakee Center	Kankakee, IL	48 bags	8/6/08	649801860683616 649801860683623 649801860683630 649801860683647 649801860683654 649801860683661 649801860683678
4197	Aspirus Wausau Hospital	Wausau, WI	24 bags	8/6/08	649801860683210
4134	Parkland Medical Center	Derry, NH	24 bags	8/6/08	649801860681810 649801860681827
4094	Northern Westchester Hospital Center	Mount Kisco, NY	24 bags	8/6/08	649801860681551 649801860681520

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					649801860681537 649801860681544
4160	Northport Medical Center	Northport, AL	24 bags	8/6/08	649801860682558
4078	Samaritan Medical Center	Watertown, NY	48 bags	8/6/08	649801860681254 649801860681247 649801860681230 649801860681223
4056	West Suburban Medical Center	Oak Park, IL	24 bags	8/5/08	649801860678667 649801860678674 649801860678681 967752959111
4028	Lakewood Ranch Medical Center	Bradenton, FL	24 bags	8/5/08	649801860678100 649801860678094
4045	Provena Saint Joseph Medical Center	Joliet, IL	72 bags	8/5/08	649801860677929 649801860677912 649801860677905 649801860677899 649801860677882 649801860677875 649801860677868
3950	Sherman Hospital	Elgin, IL	48 bags	8/5/08	649801860676632 649801860676625
3952	Swedish Covenant Hospital	Chicago, IL	24 bags	8/5/08	649801860676649

MANUFACTURING CODES

Ms. Cerullo stated Ameridose uses PK Software, generic pharmacy software, which randomly assigns lot numbers. The firm's lot numbers are not specific to a date or batch sequence, each batch (in-process and finished product) has a unique lot number.

DEVIATION

A photocopy of Deviation No. D08118 was collected and attached as *Exhibit 13*. This deviation was noted during finished product preparation of Fentanyl/Ropivacaine in 0.9% NaCl 1 mcg/0.2% 100mL Injectable Bag, Lot 07162008@166. The pharmacy technician inadvertently spiked the Fentanyl Stock Solution bag with the tubing set that had been used in the Ropivacaine bag. The pharmacist was notified immediately and the Fentanyl Stock Solution that was contaminated was

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scrapped to waste. There was no product impact reported. The root cause of the deviation was human error.

STERILITY POSITIVE

Ms. Cerullo stated the firm has received one positive sterility result. A photocopy of Out-of-Specification No. OOS08052 was collected and attached as *Exhibit 14*. This positive sterility result for Day 14 (June 16, 2008) Fentanyl 50 mcg/mL, Lot 05292008@74 was investigated and concluded to be due to an error on the part of DYNALABS.

GENERAL DISCUSSION WITH MANAGEMENT

Ms. Cerullo reported finished product shelf life ranges from 14 to 90 days, based on the product. Fentanyl Citrate in 0.9% NACL 10mcg/mL Injectable bags are labeled with a 45 day shelf life. Oxytocin added to 0.9% NACL 30 units/500mL Injectable bags are labeled with a 90 day shelf life.

Ms. Cerullo confirmed that the firm has not performed a sterilization validation study. She stated the firm tests the stock solution for sterility and performs integrity testing on the filter used after preparing the lot. Mr. Cerullo and Mr. Conigliaro explained that "every time the product is made the stock solution is validated, because it is tested for sterility". They noted that if the firm was to validate the process this is what it would do.

Ms. Cerullo presented a Bag Overfill Study Summary which was performed to evaluate the overfill associated with 100 mL Hospira Normal Saline bags. A photocopy of the Summary was collected and attached as *Exhibit 15*. Ms. Cerullo explained this study was used to determine the volume of sodium chloride to extract prior to adding stock solution to the product bag. This evacuation and addition is outlined in the manufacture worksheet for finished product Fentanyl Citrate in 0.9% NACL 10mg/mL 100mL Injectable bag, Lot 07302008@4. Refer to *Exhibit 6, Page 1*.

Mr. Conigliaro stated a written response to the Form FDA 483 was submitted on or about August 22nd. He noted that as part of the response the firm has committed to implement identity testing of its finished products. Ms. Cerullo stated SOP No. 6.021 version 1.0 entitled, "QA Sample Process and Library" was effective at the time of the previous inspection. She explained that the firm has revised SOP No. 6.021 to version 2.0 and is in the process of training employees on the new version. A photocopy of SOP No. 6.021 version 1.0 and 2.0 was collected and attached as *Exhibit 16a-b*.

A Form FDA 463a Affidavit was signed by Gregory A. Conigliaro, General Manager/Vice President. A Form FDA 483 was not issued and additional samples were not collected.

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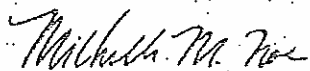
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ATTACHMENTS

Form FDA 482 Notice of Inspection dated 9/15/08 issued to Gregory A. Conigliaro, General Manager/Vice President	1 pg
Form FDA 482 Notice of Inspection dated 9/17/08 issued to Gregory A. Conigliaro, General Manager/Vice President	1 pg
Form FDA 463a Affidavit dated 9/18/08 issued to and signed by Gregory A. Conigliaro, General Manager/Vice President	5 pgs

EXHIBITS COLLECTED

1	Ameridose Organizational Chart	1 pg
2	Raw Material: Fentanyl Citrate Powder-USP - Lot 66559A	5 pgs
3	Concehtrate: Fentanyl Concentrate in H ₂ O 10mg/mL, Lot 07012008@96	6 pgs
4	Stock Solution: Fentanyl (as Citrate) in SWFI 50mcg/mL 4000mL Stock Solution Lot 07082008@109	11 pgs
5	Stock Solution: Fentanyl (as Citrate) in SWFI 50mcg/mL 4000mL Stock Solution Lot 07142008@109	14 pgs
6	Finished Product: Fentanyl Citrate in 0.9% NACL 10mg/mL 100mL Injectable bag, Lot 07302008@4	6 pgs
6a	Label Example: Fentanyl Citrate in 0.9% NACL 10mg/mL 100mL Injectable bag	2 pgs
7	Orders/Shipment: Fentanyl Citrate in 0.9% NACL 10mcg/mL Lot 07302008@4	13 pgs
8	Raw Material: Oxytocin, USP (non-sterile active powder) Lot XA0048	4 pgs
9	Stock Solution: Oxytocin in SWFI 10 units/mL 4000mL Stock Solution, Lot 07102008@83	12 pgs
10	Finished Product: Oxytocin added to 0.9% NACL 30 units/500mL injectable bag, Lot 08022008@54	6 pgs
11	Label Example: Oxytocin added to 0.9% NACL 30 units/500mL injectable bag	1 pg
12	Orders/Shipment: Oxytocin added to 0.9% NACL 30 units/500mL injectable bag, Lot 08022008@54	29 pg
13	Deviation No. D08118	3 pgs
14	Out-of-Specification No. OOS08052	14 pgs
15	Bag Overfill Study Summary 100 mL Hospira NS Bag	4 pgs
16a	SOP No. 6.021 version 1.0 entitled, "QA Sample Process and Library"	4 pgs
16b	SOP No. 6.021 version 2.0 entitled, "QA Sample Process and Library"	9 pgs

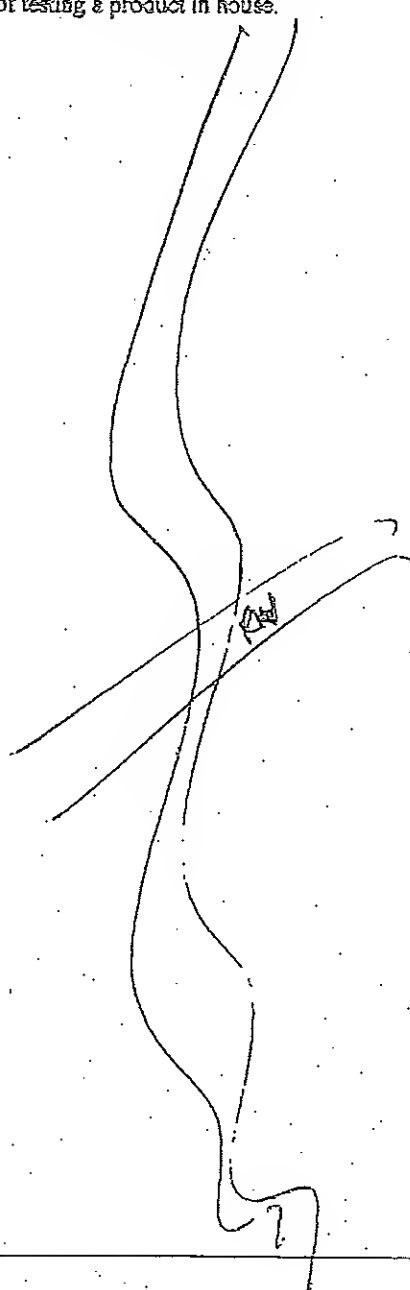

Michelle M. Noe, Investigator

FDA 483 and Inspection Report for Ameridose

(Jul./Aug. 2008)

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DIRECT ADDRESS AND PHONE NUMBER One Montvale Avenue Stoneham, MA 02180 (781) 596-7700 Fax: (781) 596-7896		DATE(S) OF INSPECTION 07/21/2008 - 08/06/2008* FB NUMBER 3005881167	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS MADE TO: Mr. Gregory A. Conigliaro, General Manager			
FIRM NAME Ameridose LLC CITY, STATE, ZIP CODE, COUNTRY Framingham, MA 01702-6211		STREET ADDRESS 50 Fountain St. TYPE ESTABLISHMENT INSPECTED Drug Manufacturer	
<p>This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss this objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.</p>			
<p>DURING AN INSPECTION OF YOUR FIRM I OBSERVED:</p> <p>OBSERVATION 1</p> <p>Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.</p> <p>Specifically, the firm manufactures stock solution of an additive made from an Active Pharmaceutical Ingredient received and performs a potency, sterility, and endotoxin testing on the additive, and then manufactures an Admixture for review and release by the Clean Room Pharmacist and Freight Room Pharmacist prior to shipment. There is no potency or identity test done on the finished drug product, and the product is shipped immediately and prior to the 14 day sterility test results are received by the firm. Three examples are as follows: a) Fentanyl/Bupivacaine in 0.9% NaCl Lot#07152008@134 manufactured on 7/16/08 and shipped immediately; b) Sufentanil/Ropivacaine 0.4 mcg/0.2% ml Cassette Lot#07082008@136 manufactured on 7/09/08 and shipped immediately; and c) Oxytocin added to LR 20 units/ 1000 ml INJ BAG Lot#07142008@3 manufactured on 7/14/08 and shipped on 7/16/08. The firm SOP 9.060 Sterility Product Process VER 1 dated 7/17/06 under 9.0 PROCEDURE reveals the statement at 9.1.5 "Due to limited Beyond Use dating on our products, products free of contamination... shall be released on day THREE by the quarantine Pharmacist".</p> <p>OBSERVATION 2:</p> <p>Written procedures are lacking which describe in sufficient detail the identification, sampling, testing, approval, and rejection of components.</p> <p>Specifically, SOP 5.010 Product Procurement, Receipt and Inspection Version 1.0 dated 7/17/06 does not address how the received active pharmaceutical ingredients are sampled, tested and identified by a test method shown in the USP or verified and validated to be equivalent to a known method in the USP. The firm receives a Certificate of Analysis on the Active Pharmaceuticals received and has validated the test results on the Certificate of Analysis of the initial lots from the suppliers, along with periodic tests on future lots received; however, some but not all API lots received have a specific identity test done on them. For example, the active pharmaceuticals for Hydromorphone HCL Lot#65723/C and 65300/E, and Ropivacaine 64719 were received by the firm and not specifically identity tested by test methods shown in the USP.</p>			
SEE REVERSE OF THIS PAGE		<div style="text-align: right;"> DATE ISSUED 08/06/2008 </div>	
<small>FORM FDA 483 (6-02)</small>		<small>PREVIOUS EDITION OBSOLETE</small> INSPECTIONAL OBSERVATIONS <small>PAGE 1 OF 4 PAGES</small>	

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT ADDRESS AND PHONE NUMBER One Montvale Avenue Stoneham, MA 02180 (781) 596-7700 Fax: (781) 596-7896		DATE(S) OF INSPECTION 07/21/2008 - 08/06/2008*	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Gregory A. Conigliaro, General Manager		FBI NUMBER 3005881167	
FIRM NAME Ameridose, LLC		STREET ADDRESS 50 Fountain St	
CITY, STATE, ZIP CODE, COUNTRY Framingham, MA 01702-6211		TYPE ESTABLISHMENT INSPECTED Drug Manufacturer	
<p>OBSERVATION 3</p> <p>The master production and control records are deficient in that they do not include a statement of theoretical yield and minimum, maximum, and yield percentages.</p> <p>Specifically, a review of two Master Production records (Master Formula Worksheets) revealed no statement of theoretical yield nor a percentage range of theoretical yield that the produced batch should fall within. This can be seen in the following two Master production (Formula Worksheet) examples: a) Fentanyl (as citrate) in SWFI 50 mcg/ml 4000 ml Stock Solution, and b) Oxytocin in SWFI 10 units/ml 4000ml Stock Solution.</p>			
<p>OBSERVATION 4</p> <p>Batch production and control records do not include results of the inspection of the packaging and labeling area before and after use for each batch of drug product produced.</p> <p>Specifically, a review of Batch Formula Worksheets for both stock solution and finished product revealed that the firm does not document the line clearance inspection of the packaging and labeling area before and after use. For example, a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#05172008@130 made 6/18/2008, and b) Oxytocin added to LR 20 units/1000 ml INJ BAG Lot#07162008@13 made 7/16/08 do not include instructions or have documented a line clearance before and after the packaging and labeling of the products involved.</p>			
<p>OBSERVATION 5</p> <p>The batch production and control records are deficient in that they do not include a statement of the actual yield and percentage of theoretical yield.</p> <p>Specifically, a review of Batch Formula Worksheets for both stock solution and finished product revealed that the firm does not have a statement of the actual yield and the percentage of theoretical yield at the completion of the process. For example, there is no actual yield or percentage of theoretical yield noted in the following two Formula Worksheets: a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#05172008@130 made 6/18/2008 (Step#7 & 13), and b) Oxytocin added to 0.9% NACL 30 units/ 500 ml INJ BAG Lot#07162008@27 for 432 bags made 7/16/2008 (Step#4).</p>			
<p>OBSERVATION 6</p> <p>Written production and process control procedures are not followed in the execution of production and process control functions.</p> <p>Specifically, during the review of several SOPs it was noted that the firm was not following what was expected as noted in the following two documents:</p> <p>a) SOP 9.100 Sterile Technique Qualification (Media Fills) VER 2 dated 6/16/08 under 10.12 response to Positive results refers to "retraining" only throughout the section, and does not refer to the firm's Out of Specification Procedure SOP 3.030 for positive test result follow-up; and b) SOP 6.021 Quality Assurance Sample Process and Library VER 1 dated 6/11/07</p>			
SEE REVERSE OF THIS PAGE		<div style="text-align: right;"> 08/06/2008 </div>	
FORM FDA 483 (04/03)		<div style="display: flex; justify-content: space-between;"> PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 2 OF 4 PAGES </div>	

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT ADDRESS AND PHONE NUMBER		DATE OF INSPECTION	
One Montvale Avenue Stoneham, MA 02180 (781) 596-7700 Fax: (781) 596-7896		07/21/2008 - 08/06/2008*	
NAME AND TITLE OF FDA/CDC TO WHOM REPORT ISSUED		FD NUMBER	
TO: Mr. Gregory A. Conigliaro, General Manager		3005881167	
FIRM NAME		STREET ADDRESS	
Ameridose LLC		50 Fountain St	
CITY, STATE, ZIP CODE, COUNTRY		TYPE ESTABLISHMENT INSPECTED	
Framingham, MA 01702-6211		Drug Manufacturer	
<p>reveals under 9.4 Testing of Q A Sample a section on "lot samples for in house Lab testing" when there is currently no in house lab testing or capabilities of testing a product in house.</p> 			
SEE REVERSE OF THIS PAGE		DATE ISSUED	
		08/06/2008	
FORM FDA 602 (6-02)		PREVIOUS EDITION OBSOLETE	
INSPECTIONAL OBSERVATIONS		PAGE 3 OF 4 PAGES	

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER

One Montvale Avenue
Stoneham, MA 02180
(781) 596-7700 Fax: (781) 596-7896

DATE(S) OF INSPECTION

07/21/2008 - 08/06/2008*

FD NUMBER

3005881167

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Mr. Gregory A. Conigliaro, General Manager

FIRM NAME

Ameridose LLC

STREET ADDRESS

50 Fountain St

CITY, STATE, ZIP CODE, COUNTRY

Framingham, MA 01702-6211

TYPE ESTABLISHMENT INSPECTED

Drug Manufacturer

* DATES OF INSPECTION:

07/21/2008(Mon), 07/22/2008(Tue), 07/23/2008(Wed), 07/28/2008(Mon), 07/29/2008(Tue), 07/30/2008(Wed), 08/04/2008(Mon),
08/05/2008(Tue), 08/06/2008(Wed)

FDA EMPLOYEE'S NAME, TITLE, AND SIGNATURE:

Richard H. Penta

Richard H. Penta, Investigator

8/6/08

SEE REVERSE
OF THIS PAGE

DATE ISSUED

08/06/2008

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SUMMARY

The firm was placed on the FY-08 New England District Work Plans as a High Risk facility and assigned under FACTS# 935703 (Attachment#1) and done in accordance with CP 7356002 Drug Process Inspection Program. The inspection covered the Quality, Production, Packaging and Labeling and Facilities and Equipment Systems at the firm. This was a follow-up to a fact finding inspection concluded 12/10/07 and is the initial drug cGMP inspection of this facility.

The firm has been drug registered since July 13, 2006 as a repacker and Other of Sterile and nonsterile mixtures and IV Admixtures. Its current drug registration is dated March 12, 2008. The firm's customers are all Hospital Pharmacy operations. While on my inspection at this facility the firm received an approved license to practice pharmacy in the state of Delaware. They now have the appropriate licenses for operations in all 50 states of the Union.

An inspection of the facility found drug cGMP issues which resulted in a List of Observations being issued to Mr. Gregory Conigliaro, General Manager on 8/6/2008. The firm manufactures stock solution of an additive made from an Active Pharmaceutical Ingredient received and performs a potency, sterility, and endotoxin testing on the additive, and then manufactures an Admixture for

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review and release by the Clean Room Pharmacist and Freight Room Pharmacist prior to shipment. There is no potency or identity test done on the finished drug product, and the finished product is shipped immediately and prior to the 14 day sterility test results are received by the firm. The firm's SOP 5.010 Product Procurement, Receipt and Inspection Version 1.0 dated 7/17/06 does not address how the received active pharmaceutical ingredients are sampled, tested and identified by a test method shown in the USP or verified and validated to be equivalent to a known method in the USP. A review of the firm's identity testing upon receipt of product reveals that, although not addressed in their SOPs, most but not all raw actives are identity tested prior to approval for use in production. The firm has received 41 active ingredients of which I requested to see 17 identity test results. The firm was able to quickly locate 11 of the 17 identity tests requested. The master production and batch history records, known as Formulary Worksheets at the firm, are deficient in that they do not have where required statements of actual yield, percentage of theoretical yield at the completion of the process, and inspection of the packaging and labeling areas before and after production. A review of several SOPs revealed that there are two firm SOPs with noted issues as follows: one that does not address the firm's Out of Specification Procedures for Media fills not meeting specifications; and a second one addressing "lot samples for in-house Lab testing" when there is currently no in-house lab testing or the capabilities of testing the product in-house.

A review of the firm's Formulary Worksheets on Lot and Batch identification numbers and SOP 9.050 Beyond-Use Dating (BUD) of Products dated 5/22/08 reveals that the firm lot and batch numbers are assigned when the Formulary Worksheet is issued; however, some are issued in the afternoon and the products are not made until the next day or sometimes after the weekend. The lot number and BUD do not change when this occurs. The BUDs (expiry date) on the Formulary Worksheets and products I reviewed range from 30 days to 150 days.

ADMINISTRATIVE DATA

Inspected firm: Ameridose LLC
Location: 50 Fountain St
Framingham, MA 01702-6211
Phone: 508-656-2653
FAX: 508-820-0644
Mailing address: 50 Fountain St
Framingham, MA 01702-6211

Dates of inspection: 7/21/2008, 7/22/2008, 7/23/2008, 7/28/2008, 7/29/2008, 7/30/2008,
8/4/2008, 8/5/2008, 8/6/2008

Days in the facility: 9

Participants: Richard H. Penta, Investigator
LCDR Dehra Emerson, Investigator

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FEI: 3005881167
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Credentials were shown and a Notice of Inspection presented to Mr. Gregory A. Conigliaro, General Manager, on 7/21/08 by Investigators Penta and LCDR Emerson in the presence of Ms. Sophia Pasedis, VP Regulatory Affairs, Compliance and Auditing, who was also shown our credentials. LCDR Emerson was present for only the first day of the inspection. A List of Observations was presented to Mr. Gregory Conigliaro, General Manager and co-owner, on August 6, 2008 at the conclusion of the inspection. On July 28, 2008 Ms Pasedis signed a FDA 463a Affidavit regarding six documentary samples collected for drug cGMPs and finished product labeling. On August 5, 2008 Ms. Pasedis signed a FDA463a Affidavit regarding two physical samples collected for sterility, potency and identification analysis. She identified the photographs of labeling, and identified and provided me with all the documents and records collected by me regarding both the documentary and physical samples.

The entire report is written by Investigator Penta.

HISTORY

The firm is a Limited Liability Corporation (LLC) that opened in 2006 as a repacker and other of sterile and non sterile mixtures and Admixtures first registered with the USFDA (July 13, 2006), and also registered with the State Board of Pharmacy (exp.12/31/09). The firm's current USFDA drug registration is dated 3/12/2008. The firm was provided a Labeler Code Number (24200) in a letter dated 9/8/06 (See Exhibit#1). The firm is also drug registered as a manufacturer with the State of Massachusetts. The last inspection of the facility was in December 2007 regarding the firm's Compounding Pharmacy Operations. It was determined at that time that the firm was solely a repacker and manufacturer of drugs for their customers, Hospital Pharmacies. The current two Managers of Record (co-owners) are: Mr. Barry Cadden and Gregory Conigliaro, Vice President and General Manager. I was provided an Organization Chart by Mr. Conigliaro during the inspection (See Exhibit#2).

The firm's operations are from 6:30 am to 6:30 pm covered by two overlapping shifts Monday through Friday. The firm currently has approximately 100 employees. Approximately 75% of the products are shipped out of state to Hospital Pharmacies. Firm management arrives at 9:00 am. Any correspondence can be addressed to Mr. Gregory Conigliaro, General Manager, who is the most responsible individual at this address.

INTERSTATE COMMERCE

The firm ships 75% of their product outside of Massachusetts. They stated that all their customers that order the products are affiliated with hospitals. The firm manufactures small orders in Lot sized batches and combines multiple orders of one specific product into Batches of finished product. None of their manufactured or repackaged products are linked to a specific patient prescription. The firm has an internet site www.ameridose.com where they advertise Nationwide Sterile Admixing services, and Oral Syringe Repackaging Services for schedule II to VI products (See Attachment#2).

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There were six documentary samples collected for cGMP and label review which show what finished products were repackaged and/or admixtures manufactured from stock solutions for the follow actives: Fentanyl (as citrate), Hydromorphone HCL, Morphine Sulfate, Bupivacaine HCL, Ropivacaine HCL, and Oxytocin. There were also two physical samples Fentanyl in 0.9% NACL, 100 ml in 100 ml Injectable Bags, and Oxytocin 30 Units added to 500 ml 0.9% NACL Injection in a 500 ml Injectable Bag. These products have been shipped over the United States including to Illinois and Texas.

JURISDICTION

The firm currently markets over 600 products including 7 Antibiotics classes, 15 Class II, 1 Class III, 2 Class IV, and many Class VI products as noted in a 7/10/2008 Listing provided by the firm (See Exhibit#3). The firm also provided a list of 38 finished product batches that they have manufactured and distributed in the past (See Exhibit#4). The firm has identified all the products manufactured and repackaged by them with an NDC number. Ms. Pasedis, when asked, stated that a person by the name of Mark told her back in 2006 that she did not have to drug list all her products. I told her that she should call CDER drug registration and Listing Branch to discuss with someone about her firm's need to drug list all their products because they are registered as a manufacturer and repacker of drug products and Admixtures.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

The following individuals were met during the inspection and provided me with information and/or documents for review during my inspection of the facility:

Gregory A. Conigliaro, General Manager, is overall in charge of the entire operations. He provided me with answers to many questions and directed others to get information and documents to me. Ms. Pasedis and Ms. Cerullo report directly to him. Mr. Conigliaro stated during the inspection that there were two DEA persons present to conduct an inventory and inspection. He left the room and upon his return later in the day stated that the DEA agents did an inventory of the scheduled products and reviewed security.

Sophia Pasedis, VP Regulatory Affairs, Compliance and Auditing, oversees those in charge of the narcotics inventory, Quality Control and the Pharmacists who review and release the finished products. She is the one who developed all the NDC numbers for all their products. Ms. Pasedis stated during the DEA inspection that as the Pharmacist of record all other pharmacists at the firm report to her.

Melanie Cerullo, Director of Quality, was gone many times to obtain documents requested. She is quite knowledgeable in the overall operations of quality and the processing of the products.

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Vira Ajgaonkar, RPh is in charge of overseeing the receipt, dispensing, and reconciling of all the narcotics used in log books maintained for DEA review. She pointed out and provided the narcotic products and labeling as requested.

FIRM'S TRAINING PROGRAM

The firm has a Training Program in which they follow SOP 2.010 Training Program dated 1/28/08 (See Exhibit#5). The SOP under 6.0 Frequency of New Hire Training and 10.4 GMP/USP/QS Training and in-Services refer to training as a new hire and also an annual update on drug cGMPs. A review was done on the individual training records of eight employees that worked at the facility. The review noted that the firm does its initial introduction to cGMPs. The majority of the people are new to the facility and the annual refresher course needs to be planned to capture the necessary refresher training for these relatively new employees after their one year with the firm is nearing completion. Mr. Brian O'Neill, Director of Pharmacy, did most of the cGMP training prior to Ms Cerullo arriving at the firm.

MANUFACTURING/DESIGN OPERATIONS

The firm operations revolve around orders being received from their Customers, approximately 500 Hospital Pharmacies located in 49 of the 50 states, and the resulting Lot (single order) or hatch (multiple orders) Formula Worksheets being issued by the front office repacking and/or manufacturing. The firm has signed contracts with each of their customers that specify the various products that they may be interested in purchasing. The firm follows USP 797 Pharmaceutical Compounding of Sterile Preparations and the drug cGMPs. The products manufactured are patient ready doses that are not filled on the order of a prescription but rather on the order of a Hospital Pharmacy. The orders that are received early in the morning are usually manufactured that day with orders received in the afternoon sometimes being shifted to the next day.

The firm currently has manufacturing done in two Clean Rooms and has a third one proposed but not yet built. The flow of personnel and equipment and product components come through the Class 1,000,000 (ISO 9) people room and freight room respectively and flows into the middle room, which is Class 100,000 (ISO 8). Product and components are staged in locked cages at this location until needed for use in the Clean Room, Class 10,000 (ISO 7). Product manufacturing is done under separate hoods, Class 100 (ISO 5). There are 16 hoods in Clean Room 1 and 7 hoods in Clean Room 2. The firm has an Environmental Monitoring Program following their SOP 3.030 Environmental Monitoring of Clean Room Areas, which includes personnel monitoring on a weekly basis (See Exhibit#6). The monitoring is done as follows: Personnel and Surfaces (1/week); Viable Air sampling (every 2 weeks) and Non viable Air (every 6 months). Results that exceed the Alert or Action Levels in the Sop are treated as OOS results and investigated. I reviewed the last two months of environmental testing and found the firm followed their SOP. Ms Cerullo, Director of Quality stated that the firm Gram stains any organisms found at the Action or Alert Level. The finished product is released through material ports for collection or routing down a conveyor to the Freight Room to await further review and packaging for storage and/or shipment.

Quality

A request for the firm's Master SOP List resulted in the request for 15 different SOPs which were reviewed at various time during the inspection (See Exhibit#7). The review and findings will be discussed in this report with two specifically discussed under Observation #6 regarding SOP 9.100 Sterile Technique Qualification (Media Fills) and SOP 6.021 Quality Assurance Sampling Process and Library along with SOP 8.010 Filtration and Sterilization Process. The firm does have an SOP for Method Deviations and also one for Corrective Action/Preventive Action (CAPA) Management, which they follow (See Exhibits#8 & 9). A review of Fentanyl/Ropivacaine in 0.9% NACL 1 mcg/0.2 100ml INJ bag included Deviation#D08118 dated 7/18/08 where two bags were contaminated with the wrong drug and after the investigation they were destroyed. The responsibilities of Quality and Compliance are noted in SOP 9.010 VER. 2 (See Exhibit#10), which is currently under review but signed by Sophia Pasedis, VP of Regulatory, Compliance and Auditing. Under Procedure no. 10.12 Trending the firm does a Quarterly Report on product categories covering Environmental Monitoring, Deviations, OOS, Customer Complaints and Adverse Events. I told Ms Pasedis that her firm should include any recalls or returned goods information with this quarterly review.

Initially I reviewed Formula Worksheets for Oxytocin and Fentanyl type products, and then expanded to the review of Stock Solutions and finished product Formula Worksheets manufactured or repackaged from those stock solutions. The other product Formula worksheets reviewed include Hydromorphone HCL, Morphine Sulfate, Bupivacaine HCL, and Ropivacaine HCL. These can be seen in the Documentary samples 366485/490 that I collected. I also reviewed one Ephedrine stock solution. The firm provided me with their production from Ephedrine, Fentanyl, and Oxytocin Stock Solution for the past two weeks (See Exhibit#11). The issues noted missing in the Master Production and Batch History Records, known at the firm as Formula Worksheets are discussed under Observations 4 & 5 under Objectionable Conditions.

A review of several Formulary Worksheets for both individual lots for a single customer and batches for multiple customers revealed that the firm does not always produce the product on the day that is typed into "Date made". On occasion that date is crossed out because the product is made after the expected "Date made" entry. Examples of these can be seen in the Documentary samples 366485/489 as follows:

- 1) Fentanyl Citrate 50 mcg/ml 100 ml INJ bag Lot#07162008@81 date made 7/17/08;
- 2) Hydromorphone in 0.9% NACL 0.2% mg/ml 50 ml in 60 ml INJ Syringe Lot#07032008@76 date made 7/08/08;
- 3) Morphine Sulfate in 0.9% NACL 1mg/ml 100 ml IPUMP Bags Lot#06302008@17 date made 7/2/08; and
- 4) Hydromorphone/Bupivacaine in 0.9% NACL 5 mcg/ 0.075% 250 ml IPUMP bag Lot#07082008@92 date made 7/09/08.

During my review of the consumer complaints and the sterility results on product produced and reviewed by me during the inspection I asked if any product had been recalled by the firm. Ms. Pasedis stated that they needed to recall Baxter Health Heparin diluent bags used in their production because of the recall that Baxter had on product using Chinese produced active. She also stated that the firm had received no Adverse Drug Experience complaints regarding their products. The firm

has an Alert and Action level regarding their sterility results. None of the sterility results for the Formulary Worksheet I reviewed showed results that met either of these two levels.

Production

On 7/21/08 an initial inspection of the facility was conducted to see the warehousing operation, and any ongoing production. A review of the warehousing operation during the inspection revealed how products are received, entered into the network, and forwarded to a quarantine or release area dependent on the item and documentation, including a certificate of Analysis (C of A) received from the supplier. The warehouse receiver follows SOP 5.010 Ver. 1 Product Procurement, Receipt and Inspection dated 7/17/06 and added procedures of logging product into the network that is not noted in this SOP (See Exhibit#35). I was provided by Melanie Cerullo, Director of Quality Assurance, a Version 2 Draft of this SOP 5.010 which includes a more detailed description of how one receives, handles and data enters information into the network (See Exhibit#36). The firm uses the supplier/manufacturers Lot number on the incoming product to track the ingredient through the production system. We discussed the differences between an in-house numbering system and using the supplier/manufacturers Lot number and the need to be able to track all commodities coming into the facility and being used in the production process. I was referred to this drafted document SOP 5.010 regarding receipt and testing of incoming products. This is discussed under Observation 2. Additional requirements are needed for DEA Class II controlled substances which are addressed under 10.5 not 10.4 as stated in 10.4.9 of SOP 5.010. I was provided two computer printouts (See Exhibit#37) which show what data is currently entered into the network by the warehouse personnel. I observed a hard copy list maintained by the warehouse personnel which lists all products where one is waiting for the C of A to arrive for the product received and placed in Quarantine. The firm is currently going through its two year review of all SOPs and is updating those where needed as noted in SOP 5.010 and also their SOP 2.040 Order Processing dated 7/16/06 (See Exhibit#38) which was drafted and initially reviewed on 7/18/08 under the title Order Processing and generation of Formulary Worksheet (See Exhibit#39). This provides a step by step electronic entry account of how lot and hatch orders are created into Formulary Worksheets for production.

The firm personnel were staging product in the Clean room 1 Freight Room area where the stainless steel table is used as the dividing line between incoming goods and staged for production goods (See Exhibit#12 Photo #1). Pallets of Finished Product were noted staged on the floor awaiting pick up towards the back receiving area. These were next to sanitary materials that were stored on shelving in the peripheral storage area near the Narcotics vault and Clean Room #2 (See Exhibit#12 Photo#2 & 3). These cleaning and non pharmaceutical materials were removed on order of management and placed in the upstairs warehouse area by the next day. During inspection of the production area both reconstitution and "Pooling" of the received product and manufacture of admixtures were observed. The calibration of the syringes and verification by a Pharmacist was observed prior to production of the product involved. I also observed the repackaging of Cefazolin 2g Lots into syringes. There were no personnel handling of product issues observed during the multiple days I was observing the manufacturing and repackaging of product.

During my inspection of the production area Ms. Pasedis explained that Clean Room#1 was where the Oxytocin, Magnesium and all the Narcotic products are manufactured. She stated that Clean

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Room#2 is where all the stock solutions and the High risk syringes (fatalities if misused), including High dosages, are manufactured. The firm repackages the Oral syringes in the long room in between the Freight area and Clean Room #1.

Ms Sophia Pasedis discussed with me the firm's approach to conducting a Process Validation on all the processes and a Product Verification of all the products. The firm follows the following two SOPs: SOP 5.060 Process Validation dated 7/10/08 VER 2; and SOP 9.050 Beyond-Use-Dating (BUD) of Products dated 5/27/08 VER 2 (See Exhibits#13 & 14 respectively). Although the SOPs under 10.1 Process Validation and 10.10 Product Verification refer to "Chemical and physical Characteristics" and "appearance" respectively, there is a need for an Identity Test as per the USP. This is discussed in Observation#2. Ms. Pasedis stated that the firm has 40 active processes that they have done a process validation. Some examples are the Carboy, bag, syringe, Cassette, and IPump containers that all have one or more processes, like adding or withdrawing product from an IV bag, to be validated. According to management product verification has been done on all products produced at the facility. The firm does an annual process validation on one product for Potency. A review of several examples was made during the inspection and only one Process Validation Report regarding the Uniformity of the Product Hydromorphone 10 mg/ml 50 mL in 50 mL Evacuated Bag Lot# 07232007@14 was missing the raw data entry. A request for the raw data provided Certificate of Analysis Test result that was within specifications (See Exhibit#15). A complete set of the testing data for Morphine 1mg/ml in 55 ml 0.9% NACL 60 ml BD Syringe was also reviewed and obtained (See Exhibit#16). The firm does do a periodic annual test on all the incoming active materials received and compare their test results to the Certificate of Analysis provided by the manufacturer. A review of these initial and annual review tests revealed that many but not all actives are identity tested upon receipt. Again, this is discussed under Observation#2.

The firm's stability testing program follows SOP9.050 Beyond-Use-Dating (BUD) of Products dated 5/27/08 VER 2 and is done on the 40 active processes. A review of the firm's Beyond-Use Dating of products SOP revealed that the firm does have a stability program in place for it various processes and products. A review of several stability reports was made which showed that Potency, Endotoxin and Sterility testing was done (See Exhibit#40). Other physical characteristics, like pH, are considered and for example are done as an in-process test for all stock solutions. The product verification of all products includes physical, chemical and microbiological tests (See Exhibit#15). The stability testing is done at an outside laboratory Dyna Labs St. Louis, MO. The time points for their stability testing for new finished products are: 14, 30, 45, 60, 75, 90, and 120 days for all container closure types.

The firm through its stability program provides information to the Stability Committee noted in SOP 9.050 Beyond-Use Dating(BUD) of Products dated 5/22/08 (See Exhibit#14), which they use to develop a BUD or expiration date for their many products. A review of the 6 documentary Samples and the Formulary Worksheets reviewed and collected during the inspection revealed the following for BUDs (expiration dates): 1) Fentanyl Concentrate (120 days), stock (90 days) and finished product (45 days); 2) Hydromorphone stock (90 days) and finished product (60 days); 3) Morphine Sulfate stock (90 days) and finished product (60 days); 4) Bupivacaine stock (90 days) and finished product (45 days); 5) Ropivacaine stock (90 days), finished product with Fentanyl (45 days), and finished product with Sufentanil (30 days); 6) Oxytocin stock (120 to 150 days plain or with SWFI), with Lactose Ringers (42 days), with NACL or D5W (90 days); and 6) Ephedrine (75 days). This coincides with the stability program. Ms Pasedis stated that all products on stability are run for

towards 180 days. This is so that the data can be collected and used by the Stability Committee with other data to decide on the BUD (expiry date).

The firm also has a repacking operation where they pool known product into large IV bags and then with a calibration machine repack the products into syringes. They also take stock solution that has been sterility, endotoxin, and potency tested and repack the product into syringes and/or cassettes for use at the Hospitals.

The firm does maintain a reserve sample on both refrigerated and room temperature finished products. Ms. Pasedis stated that the firm has a policy of moving to an area for disposal any products that are six months beyond expiry. The same disposal company, ESP Enterprises handles these out of date reserves.

Facilities and Equipment

A discussion was held with management regarding the Sterile Water for Injection (SWFI), equipment, and materials used by the firm to produce their products. The Formula Worksheet lists everything used under chemicals and devices. The majority of the equipment used is disposable, for example, a fluid transfer set, 0.22 micron filter and a syringe, 20 ml disposable luer lock. The stock solutions use a Carboy and some finished products are packaged in syringes and cassettes. The firm has multiple Repeater pumps (See Exhibit#17) by Baxa that are all located in Clean Room One or Two. The units are continually calibrating a set amount. The firm also has an SOP 4.060 Operation and Maintenance of Anprolene Gas Sterilizer dated 5/28/08 (See Exhibit#18) for their Anprolene Gas Sterilizer which they use to sterilize components used in the process. The firm does a Steritest on each load and records the findings on Attachment#2 Sterilization Record (See Exhibit#19). The firm brings in all the SWFI that it uses in production from an outside vendor. The firm has an outside Vendor do the testing and maintains the Air Exchange system which services the Clean rooms. Magnehelic gauges are in place outside the clean room areas to monitor the pressure differential.

Packaging and Labeling

The firm has all their labels stored on a computer where a limited number of authorized persons can access and print out the quantity requested by production for manufacturing of a lot. A specific number of extras are printed so that they can be kept with the Formula Worksheet and Quarantine/Release logs used by the office and the freight area. The firm does follow its SOP 5.040 Product Labeling dated 3/19/08 (See Exhibit#20); however, there is no mention of the need for a line clearance both before and after production, including the documentation necessary. The firm does maintain a labeling reconciliation regarding all labels issued. The firm does have an SOP 1.040 Log of Use, Maintenance, and Cleaning (LUMAC) of Equipment (See Exhibit#21), and Ms. Pasedis stated that they did have a separate log book recording line clearances at each hood; however, this was stopped on 2/4/2008. I discussed with management the lack of documenting line clearances of packaging and labeling materials under Observation #4 under Objectionable Conditions. They stated that they would update the Formula Worksheets and necessary SOPs to reflect line clearances being done and documented.

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An inspection of the Freight area where product is held for order picking and also stored in sealed cases was done throughout the inspection. The inspection revealed that some product was left in storage for longer than the day manufactured. On 7/23/08 I observed 4 cases of Oxytocin LR 20 units/ 1000 ml INJ bags made 7/8/2008 still stored in the Freight Room storage racks. A check of the Office Quarantine/Release Log showed 48 units to Baptist dated 7/9 crossed out while the Quarantine/Release Log from the Freight Room does not show Baptist but does have a Hilo entry dated 7/14 for 24 units. All other entries match (See Exhibit#22). There was still no reconciliation of the Office and Freight Log sheets on 7/23/08 for this Oxytocin lot. I discussed with Ms. Pasedis the need for the Office Quality personnel to reconcile in a timely manner the shipment of all units with any inventory in the Freight Room area. There is an Area Cleaning Log in the repacking area that noted for the July 15 through 21/2008 period that this hatch was produced on 7/8/2008. Ms. Pasedis stated that they had stopped using Cleaning logs but would reinstitute line clearance in the Formula Worksheets. On 7/23 the firm authorized the remaining four cases of product for destruction through "EXP" (EXP Pharmaceutical SVCS Corp Fremont, CA 94539. The firm follows SOP 5.050 Packaging and Shipping Process where 10.0 Procedure discusses how to prepare and handle shipments (See Exhibit#23).

MANUFACTURING CODES

The firm uses a month, day year coding system followed by a "@" and the number of hatches produced that day at the end. For example: 07092008@51 shows the product is produced on July 9, 2008 and that it is the 51st hatch made that day of all products produced in the one day. The firm also identifies all its finished drug products with an NDC number which includes the labeler code 24200 that is unique to the firm (See Exhibit#1). The firm PK software system, which is developed for Pharmacy Compounding Operations, requires them to use an Rx numbering system that then allows them to track the product lot number, NDC number, product description, and who purchased the product.

The Orders that the firm receives result in Formulary Worksheets for the lots and batches being issued with a Lot number and BUD (expiry date). Some lots and hatches issued in the afternoon are not produced until the following day or after the weekend. This results in the "date made" being different from the portion of the lot or hatch number that shows the month and day made, e.g. 0714.

COMPLAINTS

A review of the firm's SOP 9.110 Consumer Complaints dated 3/19/08 VER 2 (See Exhibit#24) and request and review of complaints received the past two months revealed that the majority were due to shipping damage. There were no ADE complaints and only three Product Experience complaints received under AC08155 dated 5/13/08, AC08156 dated 5/12/08, and AC08184 dated 7/1/08 (See Exhibit#25). Two complaints AC08155 and AC08184 on two different lots of Oxytocin did not get the expected patient response. The third complaint AC08156 was regarding labels peeling off syringes and sticking to each other. The issue was fixed by Pharmacy Technicians at the Hospital; however, the firm retired the "low" tack adhesive label and introduced a "high" tack adhesive. No

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further follow-up could be done as the pharmacy technicians could not get further response from the doctors. Written responses are normally sent as per 10.9 of the SOP.

RECALL PROCEDURES

A review of the firm SOP 9.070 Recall Procedure dated 4/11/08 VER 2 (See Exhibit#26) was reviewed. The firm has had no recall of its own; however Ms. Pasedis did relate to me how they needed to recall Baxter Health Heparin diluent bags used in their production because of the recall that Baxter had on product using Chinese produced active. The firm will conduct an investigation, document the event, and determine if a product needs to be recalled. They would then generate a Recall Notification Letter (See Attachment 1 of the SOP 9.070) for issuance, and then may additionally contact them by telephone prior to sending the hard copy Recall Notification Letter.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the identity and strength of each active ingredient prior to release.

Specifically, the firm manufactures stock solution of an additive made from an Active Pharmaceutical Ingredient received and performs a potency, sterility, and endotoxin testing on the additive, and then manufactures an Admixture for review and release by the Clean Room Pharmacist and Freight Room Pharmacist prior to shipment. There is no potency or identity test done on the finished drug product, and the product is shipped immediately and prior to the 14 day sterility test results are received by the firm. Three examples are as follows:
a) Fentanyl/Bupivacaine in 0.9% NACL Lot#07152008@134 manufactured on 7/16/08 and shipped immediately;
b) Sufentanil/Ropivacaine 0.4 mcg/0.2% ml Cassette Lot#07082008@136 manufactured on 7/09/08 and shipped immediately; and c) Oxytocin added to LR 20 units/ 1000 ml INJ BAG Lot#07142008@3 manufactured on 7/14/08 and shipped on 7/16/08. The firm SOP 9.060 Sterility Product Process VER 1 dated 7/17/06 under 9.0 PROCEDURE reveals the statement at 9.1.5 "Due to limited Beyond Use dating on our products, products free of contamination...shall be released on day THREE by the quarantine Pharmacist".

Reference: 21 CFR 211.165(a)

Supporting Evidence and Relevance:

The firm receives their Active Pharmaceutical Ingredients (Bulk Chemicals) both in the powdered state as non-sterile powders and also as finished sterile actives products from firms like Hospira, McKesson, and Samson Medical Technology (See Attachment#3). A review of SOP 9.010 Responsibilities of Quality Assurance dated 7/18/08 VER 2.0 as a draft states under 10.3.6: "Pharmacists are responsible for final approval, release, or rejection of all preparations." (See

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Exhibit#10) A review of SOP 6.021 QA Sample Process and Library VER 1.0 dated 6/11/07 (See Exhibit#27A) under 9.0 Procedure describes the sample size ("withdraw 2% of the lot quantity, a minimum of 2 preparations, a 5 ml sample"), documentation and reporting results, testing and storage of the samples obtained. The revised Version 2 of SOP 6.021 (See Exhibit#27B) under 10.4.2 states "5 ml collected in a 10 ml vial". The firm currently sends product to one of two outside laboratories for testing, mainly Dyna Labs St. Louis, MO (See Attachment#4). The firm has a program in place to test all stock solutions made in-house for Potency, Sterility, and Endotoxin. They wait the 14 days for the sterility results prior to using these Stock Solutions in production of Admixtures or repackaging into syringes or cassettes. These stability and finished product stock solution tests that they conduct are noted in SOP 9.050 Beyond-Use Dating (BUD) of Products dated 5/27/08 under 10.7.5 (See Exhibit#14).

The firm does collect the 5ml or 2% of any Admixtures produced and send them out for Sterility testing only. There is no identity or potency test performed on the finished Admixture product. A review of SOP 9.060 Sterile Product Process dated 7/17/06 under Procedure and 9.1.5 states "Due to limited Beyond Use dating on our products, products free from contamination and inspections are complete and meet all requirements, shall be released on day THREE by the Quarantine Pharmacist. Results shall be obtained until day 14." (See Exhibit#28). Ms Pasedis stated that they once did adhere to the SOP requirement of awaiting the 3 day results prior to use, but do not now. Currently the firm starts shipping the product immediately. The firm gets both a 7 and 14 day sterility result on all samples sent out for sterility testing. Ms. Pasedis stated that their contract laboratory would notify them immediately if a positive result was seen earlier than the seven day report.

The Chart below shows that the finished products were shipped immediately after production. The Pharmacist and/or Quality Assurance do not wait the three days for preliminary sterility results as per SOP# 9.060 Sterile Product Process nor the 14 days for the final sterility results from the contract laboratory, Dyna Laboratories St. Louis, MO. The products listed below, save one, were collected as documentary samples 366485 through 366490 as all six were manufactured from non-sterile active powders. The other product, Oxytocin added to LR 20 Units/ 1000ml INJ bag was made from a known source of a sterile product received by the firm.

Sample No.	Product	Lot No.	Mfgr. Date	Start Ship Date	End Ship Date	14 Day Sterility Result	Lah Lot No.
366486	Hydromorphone HCL	070322008@10	7/8/08 Repacker	7/7/08	7/10/08	7/28/08	07092008Y1
366488	Hydromorphone HCL/Bupivacaine	07082008@92	7/9/08	7/09/08	Only 1	7/25/08	07102008Y5
366489	Sufentanil/ Ropivacaine	07082008@136	7/9/08 Mfgr.	7/10/08	Only 1	7/28/08	07112008Y 3007142008A
Exhibit31	Oxytocin	07142008@3	7/14/08	7/16/08	7/16/08	7/30/08	07152008A
366485	Fentanyl	07162008@81	7/17/08	7/17/08	Only 1	8/4/08	07182008Y3
366487	Morphine Sulfate	06272008@153	6/30/08 Repacker	6/27/08	7/15/08	7/21/08	07032008Y1

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Sample No.	Product	Lot No.	Mfgr. Date	Start Ship Date	End Sship Date	14 Day Sterility Result	Lab Lot No.
366485	Fentanyl/ Bupivacaine	07152008@134	7/16/08	7/17/08	Only 1	8/4/08	07182008Y3
366490	Oxytocin	07162008@13	7/16/08	7/18/08	7/21/08	8/4/08	07182008A
Exhibit32	Oxytocin	07112008@102	7/11/08	7/11/08	Only 1	7/29/08	07142008A

The Sterility Test Results for the above lots in Table 1 were received by the Contract Laboratory after the 14th day. All shipments were shipped prior to the 14 sterility testing results were complete and provided to the firm (See Exhibit#29). The Oxytocin 10 units/ml vial injectable Lot#404669 manufactured by Abraxis Grand Island, NY was used to make the Stock Solution of Oxytocin Lot#07112008@35 (See Exhibit#30), and the Abraxis Oxytocin package insert labeling stored in the narcotics vault was collected. Oxytocin Lot#07142008@3 noted in the above table was produced using this Oxytocin Stock solution Lot#07112008@3 (See Exhibit#31). The Oxytocin Lot#07112008@102 was shipped immediately on 7/11/08 although the sterility test results were not in until 7/29/08 (See Exhibit#32). The Ephedrine Sulfate Lot# 62425 DD comes from Hospira Franklin, MA as a sterile product in ampoules and was used to make an Ephedrine Stock Solution Lot#07082008@114 on 7/10/2008 and sterility tested under Dyna batch No. 07112008D and found to be negative. The product was used in the manufacture of finished product from 7/10 through 14/08 (See Exhibit#33). There were also two physical sample collected 366491 10 mcg/ml Fentanyl in 0.9% NACL 100 ml, and 366492 Oxytocin 30 units added to 500 ml 0.9% NACL, which were also released for shipment prior to a 3 or 14 day stability result being received.

Discussion with Management:

A discussion with Ms Pasedis and Mr. Conigliaro was held during the inspection. We discussed how they did test the Stock Solutions for Potency, Sterility and Endotoxin. Those stock solutions that are solely repackaged into syringes or cassettes are basically the same product. I discussed with them that at minimum an identity and potency or strength test is needed along with a sterility test for any sterile products. They stated that they currently do a sterility test on all Admixtures and products manufactured. This is done at Dyna Labs where they pool the product samples into groups and do a membrane filtration test on the pooled products and provide the firm with the results at 7 and 14 days. Ms. Pasedis stated that they stopped holding the finished product for three days in order to get a preliminary sterility result because of the short shelf life of the products along with their Customers who wanted the maximum amount of time to use the product they ordered. At the conclusion of the inspection Management stated that they would respond within 10 to 14 days and that they expected to have a plan to address the need for finished product testing. The firm provided me with a new draft of SOP 6.021 QA Sample Process and Library where they eliminated the reference to in-house testing of samples collected. All samples are sent out to a contract laboratory. The firm only does Environmental testing in-house at their small laboratory next to the Offices in the main building (See Exhibit#34). The correction of this SOP is mentioned in Observation #6.

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The firm provided me with a Draft of a Final Preparation Specification for Hydromorphone 0.2mg/ml in 50 ml 0.9% Sodium Chloride 60 ml BD Syringe NDC 24200-297-80. This document provides an Appearance Specification, label specification, Visual identification, Physical tests, and Final Preparation Strength (See Exhibit#34). This was provided by Ms Pasedis who stated that they are in the process of creating Final Preparation Specification documents for their products. Mr. Conigliaro stated at the end of the inspection that he expects to be one of the first in the industry to find a way to test his finished product preparations.

OBSERVATION 2

Written procedures are lacking which describe in sufficient detail the identification, sampling, testing, approval, and rejection of components.

Specifically, SOP 5.010 Product Procurement, Receipt and Inspection Version 1.0 dated 7/17/06 does not address how the received active pharmaceutical ingredients are sampled, tested and identified by a test method shown in the USP or verified and validated to be equivalent to a known method in the USP. The firm receives a Certificate of Analysis on the Active Pharmaceuticals received and has validated the test results on the Certificate of Analysis of the initial lots from the suppliers, along with periodic tests on future lots received; however, some but not all API lots received have a specific identity test done on them. For example, the active pharmaceuticals for Hydromorphone HCL Lot#65723/C and 65300/E, and Ropivacaine 64719 were received by the firm and not specifically identity tested by test methods shown in the USP.

Reference: 21 CFR 211.80(a)

Supporting Evidence and Relevance:

An inspection of the warehouse, Clean Room 1, Clean Room 2 and the CII Vault for Narcotics was conducted during this inspection. A review of SOP 5.010 Product Procurement, Receipt and Inspection VER 1 dated 7/17/06 (See Exhibit#35) and SOP 9.010 The Responsibilities of Quality Assurance VER 2 dated 7/18/08 (See Exhibit#10) and discussion with Ms Pasedis and Ms Cerullo about these two documents and how they related to receipt and acceptance of materials and active products for production was done at different points during the inspection. The firm has a limited description under 9.4 Item Receipt and Inspection of SOP 5.010 dated 7/17/06 and does not mention any incoming testing or visual and physical examination of the incoming product. Under 10.5 Materials of SOP 9.010 dated 7/18/08 the firm refers to SOPs 5.010 and 6.010 (Controlled Substances) and also to what Quality Assurance and Quality Controls responsibilities are regarding these received materials. There is no mention of any incoming identification test for all actives received with a Certificate of Analysis (C of A). I explained to management that there are specific identity tests noted in the USP for the six non-sterile powders that they receive from an outside vendor with a Certificate of Analysis. I commented that without a C of A the firm is expected to do a full active ingredient specifications test on incoming products. The firm provided me with an updated Ameridose Vendors List (See Exhibit#41) which has 10 firms listed. I also received from the firm a List of Powder Lots received on the 6 powders that were the focus of my inspection (See Exhibit#42). A request for and a review of the Certificates of Analysis from outside Contract

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Testing Laboratories on the initially received powder lots (See Exhibit#43) and the follow-up lots done annually (See Exhibit#44) shows that the firm have done identity tests on many incoming materials even though not directed in their SOP to do tests on all incoming ingredients. For example, the active pharmaceuticals for Hydromorphone HCL Lot#65723/C and 65800/E, and Ropivacaine 64719 were received by the firm and not specifically identity tested by test methods shown in the USP. The firm was in the process of its two year review of all SOPs and I was provided copies of those initially reviewed and approved for circulation and final approval by their Quality Assurance Committee.

Discussion with Management:

Various discussions were held with three members of management during my inspection regarding my findings, including this issue of incoming product identity testing. I explained to them that an identity test is needed on each incoming active and product that will be used in production of their repackaged items and manufactured Admixtures. I discussed how this needs to be a specific identity test listed in the USP or a scientifically justified equivalent. Ms Pasedis stated that they did tests on all the initially received lots of product and may have done all others because of the fact that they receive the same lot of product over several shipments. I commented that they should have as a procedure the testing of every new lot of product for identity that they receive. Ms Pasedis stated that they were considering the purchase of a refractometer that they could use for identity testing of received chemical materials.

A request was made for 17 different lots of active powders out of 40 received by the firm on their six non-sterile powders. The firm provided the incoming test results on 11 that were initial or annual tests, and could not find test results on 3. One of the 17 was new and not yet in inventory for use, and I asked them to stop looking for the other two from October and November 2007. There were 21 other lots of active powders listed (See Exhibit#42) that I did not request to review. The firm provided me with a draft of SOP 2.040 Order Processing and Generation of Formulary Worksheet dated 7/18/08 in which under 10.7 Filling the Order and 10.8 Send Orders to Clean Room/Repack for preparation they discuss how to create Batch or Lot Orders and provide formulary Worksheets to the Production Area (See Exhibit#39). The firm also provided me with a draft of SOP 5.010 Procurement and Receipt of Product, Components and Consumables undated that under 10.4 Receipt of Materials it discusses how materials are accepted, C of As are obtained and reviewed, and materials are logged into the network (See Exhibit#36). The firm has also drafted a new Raw Material Specification Document. I was provided a draft for Ropivacaine Powder Specification # 38779-2431-05 which provides a Visual identification, and appearance specification for the product received (See Exhibit#45). There is no physical identity test as per the USP or equivalent listed in this document.

OBSERVATION 3

The master production and control records are deficient in that they do not include a statement of theoretical yield and minimum, maximum, and yield percentages. Specifically, a review of two Master Production records (Master Formula Worksheets) revealed no statement of theoretical yield nor a percentage range of theoretical yield that the produced batch should fall within. This can be seen in the following two Master production (Formula Worksheet) examples: a) Fentanyl (as citrate) in SWFI

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50 mcg/ml 4000 ml Stock Solution, and b) Oxytocin in SWFI 10 units/ml 4000ml Stock Solution.

Reference: 21 CFR 211.186(b) (7)

Supporting Evidence and Relevance:

The firm has their entire Master Formulary Worksheets in a program on the computer and they restrict access to that program. They also keep a hard copy approved Master Formulary Worksheet in the Director of Quality's office area. After reviewing some batch records a request was made for some Master Formulary Records for review. I reviewed two stock solutions Fentanyl in SWFI 50 mcg/ml 4000 ml stock solution (Exhibit#46) and Oxytocin in SWFI 10 units/ml 4000ml stock solution (See Exhibit#47). The review revealed that, although the firm records the product weight at steps # 6 and 7 for the Oxytocin and Fentanyl respectively, and also the total number of bags filled at Steps 12 and 13 for Oxytocin and Fentanyl respectively, they do not list and expected actual yield nor a percentage range of the theoretical yield at these two steps of the operation.

I also requested and received two finished product Master Formulary Records to document the various steps and information in these master records. My review confirmed that the firm did not have a statement of the expected theoretical yield in the Master Formulas for Fentanyl/Bupivacaine in 0.9% NACL 10 mcg/0.1% 50 ml in 60 ml INJ Syringe 1 syringe (See Exhibit#48) and Oxytocin added to LR 20 units/1000 ml INJ bag 1 bag (See Exhibit#49). This is also seen in Documentary Sample 366485 where lot size for Fentanyl/Bupivacaine in 0.9% NACL 10 mcg/0.1% 50 ml in 60 ml INJ Syringes was 100 syringes to one customer. The firm states the batch size is 100 syringes to be made but does not record the actual number of units manufactured at the end of Steps 4 through 6, and does not have a percentage of theoretical yield that is expected (See Documentary Sample 366485 dated 7/28/08).

Discussion with Management:

I discussed with Ms Pasedis and Mr. Conigliaro the need to document the number of units produced and also to determine an actual yield and to compare it to the percentage of theoretical yield that is expected from the process. Ms Pasedis stated that it is a DEA requirement to track the yield of all Class II- IV products. The firm has established a range of 10-20% loss on Fentanyl, due to the double handling of the concentration (See C/R 366485). The firm has determined a Hydromorphone loss of 2 to 12 %. The firm keeps this in a separate tabulation and does it for all their products. The information is not currently used to provide a theoretical range in the master or batch formulary records.

OBSERVATION 4

Batch production and control records do not include results of the inspection of the packaging and labeling area before and after use for each batch of drug product produced.

Specifically, a review of Batch Formula Worksheets for both stock solution and finished product revealed that the

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firm does not document the line clearance inspection of the packaging and labeling area before and after use. For example, a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 made 6/18/2008, and b) Oxytocin added to LR 20 units/1000 ml INJ BAG Lot#07162008@13 made 7/16/08 do not include instructions or have documented a line clearance before and after the packaging and labeling of the products involved.

Reference: 21 CFR 211.188(b) (6).

Supporting Evidence and Relevance:

A review was made of several Formulary Worksheets of both stock solutions and finished product syringes and Admixtures in Injectable bags. The Formulary Worksheets show steps where labels are staged and reconciled in Steps 8 and 9 of the Formulary Worksheet for Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 (See Exhibit#50); however, there is no record of a line clearance before or after the production and labeling process starts. This can also be seen in the various Documentary Samples (366485/490) collected on 7/28/08 where the finished products produced from the stock solutions do not show any documentation of line clearance. One example is Oxytocin Added to LR 20 Units/ 1000 ml INJ Bag Lot#07162008@13 made 7/16/08 which is part of documentary sample No: 366490. I discussed the issue of line clearances with Ms Pasedis. The firm in the past maintained Cleaning logbooks which included the recording of line clearances at each Hood in the clean room. This was changed near the start of this year. The firm has SOP 1.040 The Log of Use, Maintenance, and Cleaning (LUMAC) of Equipment VER. 2 dated 2/4/08 (See Exhibit#21) which covers the cleaning and maintenance of Hoods and pumps, various storage equipment, and general equipment. This is separate from any labeling and packaging line clearance that is needed before and after each lot or batch is produced. The firm also has SOP 5.040 Product Labeling VER. 4 dated 3/19/08 (See Exhibit#20), which addresses the label generation, accuracy, and reconciliation of the product. The label reconciliation is completed after the product is packaged and brought to the Freight Room floor for final disposition. This does not cover line clearances inside the hoods in the Clean rooms. An inspection of Clean Room #1 on two occasions resulted in seeing the Technicians and Pharmacist producing the products and clearing the areas prior to the next lot of batch were produced; however, there was no documentation showing the line clearance of the areas.

Discussion with Management:

On July 30th I discussed with Ms Pasedis how the firm has handled the labeling of the products and the line clearance and maintenance and cleaning of the equipment, including the hoods in the clean room. She stated that the firm prior to 2/4/08, when they revised SOP 1.040 The Log of Use, Maintenance, and Cleaning (LUMAC) of Equipment VER. 2 dated 2/4/08 (See Exhibit#21), the firm followed the LUMAC SOP which required a line entry every time that the hood was cleaned prior to a new product being introduced to each of the hoods located in the two clean rooms. We discussed different ways of reintroducing the documentation of these cleanings and line clearances, including putting a line item at the start and completion of each production run so that the Admixing Technician can sign off on these actions.

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OBSERVATION 5

The batch production and control records are deficient in that they do not include a statement of the actual yield and percentage of theoretical yield.

Specifically, a review of Batch Formula Worksheets for both stock solution and finished product revealed that the firm does not have a statement of the actual yield and the percentage of theoretical yield at the completion of the process. For example, there is no actual yield or percentage of theoretical yield noted in the following two Formula Worksheets: a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 made 6/18/2008 (Step#7 & 13), and b) Oxytocin added to 0.9% NACL 30 units/ 500 ml INJ BAG Lot#07162008@27 for 432 bags made 7/16/2008 (Step#4).

Reference: 21 CFR 211.188(b) (7)

Supporting Evidence and Relevance:

Several Formulary Worksheets were reviewed at the start and during the inspection which revealed that the firm did have a lot or hatch size posted at the start and on each page of the Formula Worksheet; however, there is no actual yield or percentage of theoretical yield noted in the following two Formula Worksheets: a) Oxytocin in SWFI 10 units/ml 4000 ml Stock Solution Lot#06172008@130 made 6/18/2008 (Step#7 & 13) (See Exhibit#50), and b) Oxytocin added to 0.9% NACL 30 units/ 500 ml INJ BAG Lot#07162008@27 for 432 bags made 7/16/2008 (Step#4), which is included in Documentary Sample#366490. In regard to the Stock Solutions, the firm calculates under Step#7 the actual weights of the diluent and active, but does not determine the actual size of the hatch produced. There also is no theoretical range listed to compare with the actual amount of stock solution produced. The example provided is Exhibit#50 of Oxytocin in SWFI Lot#06172008@130 where the batch size is 20 Liters and they write in that 19101 ml is made. Although, in this case, the active is less than .5 g and would be rounded down, the weight of the finished stock solution is C (Active, Carboy, and Diluent) - A (Carboy Weight) or 19101.4 g, which rounds to 19101g or ml. This is 95.5% of the theoretical yield from a batch of 20 L. The 5 hags filled are documented under Step#13;

A review of a finished product like the Oxytocin added to 0.9% NACL 30 units/ 500 ml INJ BAG Lot#07162008@27 for 432 hags made 7/16/2008 (Documentary Sample#366490) or Hydromorphone in 0.9% NACL 0.2mg/ml 30 ml in 30 ml glass syringe Lot#07032008@10 for 350 syringes manufactured 7/8/08 (Documentary Sample#366486) shows a hatch yield of 350 typed in on each page but no actual amount made written in by the Admixing Technician under Step#4. There is also no mention of a percentage of the theoretical yield that is produced. The 432 hags of Oxytocin were produced from one lot of stock solution while the 350 syringes of Hydromorphone were produced from 3 lots of stock solution. There is no indication on either hatch record regarding the disposition of any stock solution material left over after the units of product were produced. It appears that the 1296 ml of Oxytocin and 11,200ml of Hydromorphone as listed on the Formulary Worksheet were used in the production of these respective 432 and 350 units of finished product.

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Framingham, MA 01702-6211

FBI: 3005881167
EI Start: 07/21/2008
EI End: 08/06/2008

Discussion with Management:

A discussion was held during the inspection with Ms Pasedis and Mr. Conigliaro regarding the Formulary Worksheets and the actual vs. theoretical yield of product for each stock solution and finished product produced. Ms. Pasedis stated that they know the amount of product in each stock bag at the end of the usage of each and all hags. I explained to her that they need to know the amount of product in the stock solution lot and individual hags prior to finished product production. One can use Step 7 and Step 13 to determine the amount manufactured. One can then use Step#4 in the finished product production to determine how many units are produced and how much, if any is not used, or used for a different finished product. I showed her that currently there is no entry by the Admixing Technician on how many units are produced by the Admix Technician using the calihrated Repeater Pump.

OBSERVATION 6

Written production and process control procedures are not followed in the execution of production and process control functions.

Specifically, during the review of several SOPs it was noted that the firm was not following what was expected as noted in the following two documents:

a) SOP 9.100 Sterile Technique Qualification (Media Fills) VER 2 dated 6/16/08 under 10.12 response to Positive results refers to "retraining" only throughout the section, and does not refer to the firm's Out of Specification Procedure SOP 3.030 for positive test result follow-up; and b) SOP 6.021 Quality Assurance Sample Process and Library VER 1 dated 6/11/07 reveals under 9.4 Testing of Q A Sample a section on "lot samples for in house Lah testing" when there is currently no in house lab testing or capabilities of testing a product in house.

Reference: 21 CFR 211.100(b)

Supporting Evidence and Relevance:

A request for the firm's Master SOP List resulted in the request for 15 different SOPs which were reviewed at various time during the inspection (See Exhibit#7). The review of the SOPs throughout the inspection revealed that the firm was going through a review process of all SOPs. Melanie Cerullo, Director of Quality was initiating and Sophia Pasedis, VP of Regulatory Affairs, Compliance and Auditing was doing the initial sign off prior to full QA Committee final review. A review of SOP 9.100 Sterile Technique Qualification (Media Fills) VER 2 dated 6/16/08 under 10.12 Response to Positive Results (See Exhibit#51) revealed a referral to "retraining" only throughout the section, and does not refer to the firm's Out of Specification Procedure SOP 3.030 for positive test result follow-up. This was pointed out to management who in turn drafted a version 3 of the SOP 9.100 in which they added reference to the OOS firm documents (See Exhibit#52), and provided me with the pertinent pages containing Section 10.12.

A review of SOP 6.021 Quality Assurance Sample Process and Library VER 1 dated 6/11/07 reveals under 9.4 Testing of Q A Sample, a section 9.4.3 on "lot samples for in house Lah testing" when there is currently no in house lah testing or capahlilities of testing a product in house (See

Establishment Inspection Report
Ameridose LLC
Framingham, MA 01702-6211

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Exhibit#27A). The firm drafted a new SOP 6.021 Version 2 and provided me a copy that showed that the firm had rewritten the SOP and eliminated references to in-house laboratory testing, by eliminating the Section 9.3.1 and 9.4.1.

Discussion with Management:

During the inspection discussions were held with Sophia Pasedis and Melanie Cerullo regarding various SOPs. It was brought to my attention that Ms. Cerullo was in the process of doing a review on all SOPs as per their firm policy of reviewing all documents once every two years. This has led to different SOPs that are in the draft stage, signed and dated 7/18/08 by Sophia Pasedis and undergoing final review and full QA Committee sign off. I was provided drafts showing corrections made on the above two mentioned documents.

Another document that was reviewed and discussed with all three management persons accompanying me during this inspection was SOP 8.010 Filtration Sterilization Process VER 2 dated 6/26/08 (See Exhibit#53), which is a revision to Version 1 dated 7/17/06 (See Exhibit#54). Under the Procedure Section 9.2.7 of Version 1 it states "An integrity (buhhle test) shall be performed. When I asked firm management present with me during the inspection for documentation of previous buhhle point tests conducted they were unable to provide me with any documentation that the buhhle test was performed prior to 6/26/08. Ms. Pasedis confirmed that when they revised SOP 8.010 in June 2008 they started doing buhhle point tests and included the documentation in with the Formulary Worksheet. This can be seen in Morphine Sulfate in 0.9% NACL 1 mg/ml 4000ml Stock Solution Lot#06302008@122 manufactured 7/1/2008 (See Exhibit#55) where Attachment#1 Post-Use Buhhle Point Filter Integrity Testing of Filters for Filter Lot# C8CN52423 used in production of Filter Sterilized Lot#06302008@122 passed.

REFUSALS

There were no refusals on cGMP document requests. I did request an actual or the template of the type of contracts used with their customers, which are solely Hospital facilities. Ms. Pasedis stated and Mr. Conigliaro concurred that there was no cGMP regulation that required them to provide me with either a template contract or signed contract that they have with any of their clients.

GENERAL DISCUSSION WITH MANAGEMENT

Prior to leaving on 8/5/08 I discussed with Sophia Pasedis and Gregory Conigliaro the observations that I had from my inspection to date. I also collected at this time two physical samples 366491 and 366492 with documents and submitted them for sterility, potency and identification testing. They were identified and shipped to NRL on 8/11/08.

On 8/6/08 prior to leaving the firm in the afternoon an exit discussion was held with the three management persons who accompanied me during the inspection. A List of Observations (FDA483) was issued to Mr. Gregory A. Conigliaro, General Manager, in the presence of Sophia Pasedis, VP Regulatory, Compliance and Auditing, and Melanie Cerullo, Director of Quality, after discussing two other issues with them. I discussed with the firm the following two points:

Establishment Inspection Report
Ameridose LLC
Framingham, MA 01702-6211

FBI: 3005881167
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- 1) The firm currently tracks all incoming ingredients and products used in production by the supplier/manufacturer's lot number, which they use throughout the recording of the identity of the item. The firm has some container closures and other materials that do not have lot numbers and need to be identified. Although they can continue with their current method we discussed their looking into a better method, especially when they get a new software tracking system for the documentation and production of their products; and
- 2) I discussed with them SOP 8.010 Filtration and Sterilization Process Version 2 dated 6/26/08 and the earlier Ver.1 Sterilization dated 7/17/06. The firm had no documented record that the filter integrity (bubble point) test was being done as per SOP prior to the revision of 6/28/08. They had provided me with an example of a bubble test done on 6/30/08 to show that it is now being done.

I proceeded to read each of the six (6) Observations to those present. When asked, I provided clarification and examples of what was missing in the Master and Batch Formulary Records. I also acknowledged that the firm was conducting a two year review of all SOPs and that they were in the process of updating these SOPs even before I stated my inspection. I emphasized the importance of the first observation and explained to them that my observations may lead to Regulatory Action, which includes a Warning Letter, Seizure or Injunction after prior warning. I also explained to them that the documentary samples I collected during the inspection were so that we could review the various labeling and products produced by the firm at this location. Ms Pasedis asked to whom and how soon should they respond to the List of Observations. I gave them our current District Director's name and asked that I be copied on any correspondence. They stated that they would respond within 10 to 14 days.

The inspection was concluded.

SAMPLES COLLECTED

The following two physical samples were collected:

- 1) 366491 dated 8/6/08 FENTanyl (as citrate) in 0.9% NACL, 100 ml Injectahle bags 24/10 mcg/ml units of Lot# 07302008@4 EXP September 13, 2008 collected and shipped to NRL for Sterility, Potency and identification; and
- 2) 366492 dated 8/6/08 OxyTOCIN 30 units added to 500 mL in 0.9% Sodium Chloride Injectahle bags 24 units of Lot#08022008@54 EXP November 2, 2008 collected and shipped to NRL for Sterility, Potency and Identification.

I also collected the following 6 Documentary Samples:

- 1) 366485 dated 8/6/08 Fentanyl Concentrate in Water 10mg/ml 1592.1 ml Concentrate Stock Solution Lot#06162008@31 EXP October 14, 2008 collected for cGMPs and labeling of finished product;
- 2) 366486 dated 8/6/08 Hydromorphone HCL in 0.9% NACL 0.2 mg/ml 4000 ml Stock Solution Lot#06162008@81 EXP September 15, 2008 collected for cGMPs and Labeling of finished product;
- 3) 366487 dated 8/6/08 Morphine Sulfate in 0.9% NACL 1 mg/ml 4000ml Stock Solution Lot#06112008@92 EXP September 10, 2008 collected for cGMPs and labeling of finished product;

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- 4) 366488 dated 8/6/08 Bupivacaine 0.75% 4000 ml Stock Solution Lot#06172008@125 EXP September 16, 2008 collected for cGMPs and labeling of finished product;
5) 366489 dated 8/6/08 Ropivacaine 0.5% 4000 ml Stock Solution Lot#06172008@127 EXP September 16, 2008 collected for cGMPs and labeling of finished product; and
6) 366490 dated 8/6/08 Oxytocin in SWFI 10 units/ml 4000ml Stock Solution Lot#06252008@121 EXP November 23, 2008 collected for cGMPs and labeling of finished product.

VOLUNTARY CORRECTIONS

The previous inspection concluded 12/10/2007 was not a cGMP inspection and no List of Observations was issued. The firm has corrected discussion points regarding labeling accountability on destroyed labels, listing all equipment used in production on the Formulary Worksheets; and conducting annual product reviews on their product categories.

ATTACHMENTS

- FDA482 Notice of Inspection dated 7/21/08
FDA483 List of Observations dated 8/06/2008
Attachment#1: FACTS Assignment#935703 target date 5/30/2008.
Attachment#2: List of Two Contract Servicing laboratories from 12/07 EIR
Attachment#3: List of Actives received for Production from 12/07 EIR
Attachment#4: List of two outside Laboratories from prior 12/07 EIR

EXHIBITS COLLECTED

- Exhibit#1: Ameridose Labeler Code letter dated 8/8/2006 (1 pg)
Exhibit#2: Organization Chart (1 pg)
Exhibit#3: Ameridose Products List (26 pgs)
Exhibit#4: Product Batches List (3pgs)
Exhibit#5: SOP 2.010 Training Program dated 1/28/08 (12 pgs)
Exhibit#6: SOP 3.030 Environmental Monitoring of Clean Room Areas dated 7/17/2008 (32 pgs)
Exhibit#7: Master SOP Index (3 pgs)
Exhibit#8: SOP 1.030 Method Deviations dated 1/28/2008 (9 pgs)
Exhibit#9: SOP 9.030 Corrective Action/Preventive Action (CAPA) Management dated 2/1/2008 (3 pgs)
Exhibit#10: SOP 9.010 Responsibilities of Quality and Compliance dated 7/18/2008 Draft (9 pgs)
Exhibit#11: 3 Product Stock Solution Batches July 7-21, 2008 (3 pgs)
Exhibit#12: Photos #1-3 Facility (2 pgs)
Exhibit#13: SOP 5.060 Process Validation dated 7/10/2008 (4 pgs)

Establishment Inspection Report
Ameridose LLC
Framingham, MA 01702-6211

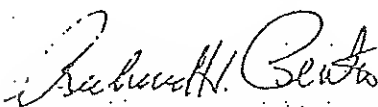
FEI: 3005881167
EI Start: 07/21/2008
EI End: 08/06/2008

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- Exhibit#14: SOP 9.050 Beyond-Use-Dating (BUD) of Products dated 5/22/2008 (5 pgs)
Exhibit#15: Product Verification report and Certificates of Analysis on Hydromorphone (C of A) (6 pgs)
Exhibit#16: Product Verification and C of A (4 pgs)
Exhibit#17: List of repeater Pumps (1 pg)
Exhibit#18: SOP 4.060 Operation and Maintenance of Anprolene Gas Sterilizer dated 5/28/08 (7 pgs)
Exhibit#19: Attachment 2 Sterilization record Cycle 79B dated 7/29/08 (3 pgs)
Exhibit#20: SOP 5.040 Product Labeling dated 3/19/08 (6 pgs)
Exhibit#21: SOP 1.040 Log of Use, Maintenance, and Cleaning (LUMAC) of Equipment dated 2/4/2008 (9 pgs)
Exhibit#22: Formula Worksheet Oxytocin added to LR 20 Units/ 1000 ml INJ bag Lot#07082008@1 made 7/8/08 and destruction comment (7 pgs)
Exhibit#23: SOP 5.050 Packaging and Shipping Process dated 6/16/2008 (5 pgs)
Exhibit#24: SOP 9.110 Consumer Complaints dated 3/19/2008 (8 pgs)
Exhibit#25: Attachment#1 Complaint Log AC08152 to 08189 and Complaints 08155/56 and 8184 (9 pgs)
Exhibit#26: SOP 9.070 Recall Procedure dated 4/11/2008 4 pgs)
Exhibit#27A: SOP 6.021 Ver. 1 QA Sample Process and Library dated 6/11/2008 (4 pgs)
Exhibit#27B: SOP 6.021 Ver. 2 QA Sample Process and Library undated draft (4 pgs)
Exhibit#28: SOP 9.060 Sterile Product Process dated 7/17/2006 (6 pgs)
Exhibit#29: Sterility Test Results on Products from 5 powdered active materials (14 pgs)
Exhibit#30: Formula Worksheet Oxytocin 10 Units/ml 1000ml stock sol Lot#07112008@35 made 7/11/08, insert label Abraxis and C of A (13 pgs)
Exhibit#31: Formula Worksheet Oxytocin added to LR 20 Units/ 1000 ml INJ Bag Lot#07142008@3 made 7/14/2008 (13 pgs)
Exhibit#32: Formula Worksheet Oxytocin added to D5W 10 Units/ 500ml INJ bag Lot#07112008@102 made 7/11/2008 w/sterility results (10 pgs)
Exhibit#33: Ephedrine 50 mg/ml 500 ml Stock Sol Lot#07082008@114 made 7/10/2008 w/sterility results (8 pgs)
Exhibit#34: Final Preparation Specification Hydromorphone 0.2 mg/ml in 50ml 0.9% NACL 60 ml BD Syringe undated Draft (3 pgs)
Exhibit#35: SOP 5.010 Ver. 1 Product Procurement, Receipt and Inspection Ver. 1 dated 7/17/2006 (2 pgs)
Exhibit#36: SOP 5.010 Ver. 1 Product Procurement, Receipt and Inspection Ver. 2 undated draft (11 pgs)
Exhibit#37: Receiving Materials electronic Log and c of a list (3 pgs)
Exhibit#38: SOP 2.040 Order Process Ver. 1 dated 7/17/2008 (4 pgs)
Exhibit#39: Order Processing and Generation of Formulary Worksheet Ver. 2 undated Draft (8 pgs)

Establishment Inspection Report
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Framingham, MA 01702-6211

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EI Start: 07/21/2008
EI End: 08/06/2008

Exhibit#40: Stability Test results as C of As (5 pgs)
Exhibit#41: List of Ameridose Vendors (2 pgs)
Exhibit#42: List of Powdered Lots received since day 1 (3 pgs)
Exhibit#43: Original Tests on incoming Actives, C of A reports (17 pgs)
Exhibit#44: Annual Tests on incoming Actives, C of A s (14 pgs)
Exhibit#45: Raw Material Specifications Ropivacaine Powder undated draft (2 pgs)
Exhibit#46: Master Formula Worksheet Fentanyl in SWFI 50 mcg/ml 4000 ml Stock Sol 1Lit size (6 pgs)
Exhibit#47: Master Formula Worksheet Oxytocin in SWFI 10 units/ml 4000 ml Stock Sol 1 Liter Size (6 pgs)
Exhibit#48: Master Formulary Worksheet Fentanyl/Bupivacaine in 0.9% NACL 10 mcg/0.1% 50 ml in 60 ml INJ Syringe 1 syringe (3 pgs)
Exhibit#49: Master Formulary Worksheet Oxytocin added to 20 Units/ 1000 ml in INJ Bag 1 Bag (3 pgs)
Exhibit#50: Formulary Worksheet Oxytocin in SWFI 10 units/ml 4000 ml Stock Sol Lot#06172008@130 made 6/18/2008 (14 pgs)
Exhibit#51: SOP 9.100 Sterile Technique Qualification (Media Fills) Ver. 2 dated 6/16/2008 (18 pgs)
Exhibit#52: SOP 9.100 Sterile Technique Qualification (Media Fills) Ver. 3 undated Draft (2pgs)
Exhibit#53: SOP 8.010 Filtration Sterilization Process Ver. 2 dated 6/26/2008 (7 pgs)
Exhibit#54: SOP 8.010 Filtration Sterilization Process Ver. 1 dated 7/16/2006 (3 pgs)
Exhibit#55: Formulary Worksheet for Morphine Sulfate 0.9% NACL 1 mg/ml 4000 ml Stock Solution Lot#06302008@122 made 7/1/2008 (3 pgs)


Richard H. Penta, Investigator

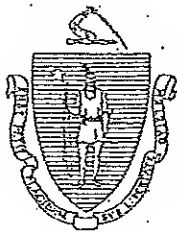
FDA Complaint Log for Ameridose, NECC, or Alaunus

FAERS search results for suspect drugs labeled as Ameridose, New England Compounding Center or Alaurus*
Reports Initially received by FDA from 1/1/02 to 9/25/12

Voluntary Reporting					
FAERS Case#	Initial FDA Rec'd Date	Reported Compounding Pharmacy	All Preferred Terms	All Reported Suspect Drugs	Reporter Selection for Box B1 Category
3823719	7/30/02	NECC	PAIN, HEADACHE	METHYLPREDNISOLONE ACETATE	Adverse Event
3824303	7/30/02	NECC	BLOOD CULTURE POSITIVE, HEADACHE, MENINGITIS, PAIN	METHYLPREDNISOLONE ACETATE	Adverse Event
3830640	8/15/02	NECC	MENINGITIS	METHYLPREDNISOLONE ACETATE	Adverse Event, Product Problem
6616697	4/7/08	Ameridose	DRUG EFFECT DECREASED, COUGH, AIRWAY COMPLICATION OF ANAESTHESIA, MEDICATION ERROR, PRODUCT QUALITY ISSUE	SUCCINYLCHOLINE CHLORIDE	Product Problem
6833736	11/21/08	Ameridose	DRUG INEFFECTIVE	PHENYLEPHRINE	Product Problem
7831464	2/8/11	Ameridose	DEVICE OCCLUSION, DEVICE LEAKAGE	HYDROMORPHONE HYDROCHLORIDE	Product Problem
8008327	6/15/11	Ameridose	MEDICATION ERROR, INCORRECT DOSE ADMINISTERED	MAGNESIUM SULFATE	Product Problem
8360445	1/24/12	Ameridose	DRUG LABEL CONFUSION, CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR, MEDICATION ERROR	FENTANYL	Adverse Event
8480382	3/23/12	Ameridose	MEDICATION ERROR, CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR, DRUG LABEL CONFUSION, PRODUCT CONTAINER ISSUE, DRUG NAME CONFUSION	MORPHINE SULFATE, HYDROMORPHONE HYDROCHLORIDE, MIDAZOLAM	Medication Error
8631046	6/12/12	Ameridose	MEDICATION ERROR, CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR, SYRINGE ISSUE	EPHEDRINE SULFATE, PHENYLEPHRINE HYDROCHLORIDE	Adverse Event
8672621	7/9/12	Ameridose	DRUG INEFFECTIVE, INCORRECT STORAGE OF DRUG, MEDICATION ERROR	SUCCINYLCHOLINE CHLORIDE	Adverse Event
Registry Reporting					
<i>Note: Registry reporting events were received for patients enrolled in a Visudyne Registry Study of Age-Related Macular Degeneration (AMD) Therapy. Per the Visudyne Registry Study protocol, adverse event reports were submitted to FDA. Product quality complaints for NECC compounded Avastin were not reported in these adverse event reports, and the adverse events were not attributed to NECC products.</i>					
FAERS Case#	Initial FDA Rec'd Date	Reported Compounding Pharmacy	All Preferred Terms	All Reported Suspect Drugs	Reporter Selection for Box B1 Category
6326386	5/25/07	NECC	DEATH	AVASTIN, VISUDYNE	Adverse Event
6326388	5/25/07	NECC	DEATH	AVASTIN, VISUDYNE	Adverse Event
6326390	5/25/07	NECC	DEATH	AVASTIN, VISUDYNE	Adverse Event
6331173	5/25/07	NECC	OVERDOSE	AVASTIN, VISUDYNE	Adverse Event
6515515	12/17/07	NECC	TRANSIENT ISCHAEMIC ATTACK	AVASTIN, VISUDYNE	Adverse Event

*No Reports were received for Alaurus

November 2012 - Ameridose 2010 Complaint



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Division of Health Professions Licensure

DEVAL L. PATRICK
GOVERNOR

TIMOTHY P. MURRAY
LIEUTENANT GOVERNOR

JUDYANN BIGBY, MD
SECRETARY

JOHN AUERBACH
COMMISSIONER

Board of Registration in Pharmacy
239 Causeway Street, Suite 500, 5th Floor
Boston, MA 02114
(800) 414-0168

<http://www.mass.gov/reg/boards/pharmacy>

June 6, 2011

James N. Czaban, Esq.
Wiley Rein, LLP
1776 K Street NW
Washington, DC 20006

RE: Complaint Docket Nos. PHA20100107 and PHA20100108

Dear Atty. Czaban:

The Board of Registration in Pharmacy (Board) has voted to resolve the above-referenced complaints by issuing a Dismissal Letter (enclosed) to Ameridose, LLC pharmacies located in Westborough, Massachusetts.

Thank you for bringing this matter to the attention of the Board.

Very truly yours,

A handwritten signature in black ink, appearing to read "Stanley B. Walczyk".

Stanley B. Walczyk, R.Ph, President
Board of Registration in Pharmacy

Encls.



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www.wileyrein.com

Received

JAN 18 2011

BOARD OF
PHARMACY

January 14, 2011

James N. Czaban
202.719.7411
jczaban@wileyrein.com

VIA UPS

James D. Coffey, Director
Board of Registration in Pharmacy
239 Causeway Street, 2nd Floor, Suite 200
Boston, MA 02114

Contains Confidential Commercial Information
and Trade Secrets; Exempt From Public Disclosure
Pursuant to Massachusetts Public Records Law, G.
L. c. 4, § 7(26)(g)

Re: Pre-Mixed Nicardipine Injection -
Notice of Settlement Between [REDACTED] and Ameridose LLC

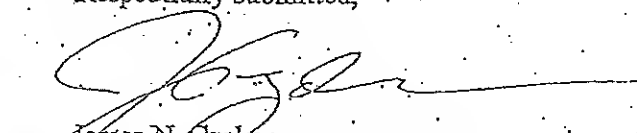
Dear Mr. Coffey:

On behalf of [REDACTED], and further to our prior
correspondence, I am writing to inform you that [REDACTED] and Ameridose LLC
("Ameridose") have reached an amicable resolution to the companies' dispute
regarding Ameridose's activities involving nicardipine.

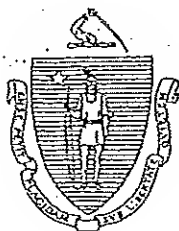
Accordingly, [REDACTED] no longer believes that any governmental investigative or
enforcement actions against Ameridose are necessary to protect the public health
and safety and hereby withdraws its request that the Board of Registration in
Pharmacy take any such actions.

We appreciate your attention to this matter.

Respectfully submitted,


James N. Czaban
Counsel to [REDACTED]

cc: [REDACTED]



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Division of Health Professions Licensure
Board of Registration in Pharmacy
Investigative Report

In the Matters of:

1. PHA-2010-0107 Ameridose, LLC, located on 50 Fountain Street in Framingham, MA (DS3467; Issued 07/13/06)

2. PHA-2010-0108 Ameridose, LLC, located on 20 Flanders Road in Westborough, MA (DS89641; Issued 11/21/08)

Manger of Record:

1. Sophia Pasedis (PH20217; Issued 06/24/1987; no prior complaints)
2. Bryan M. O'Neill (PH23692; Issued 06/23/1997; no prior complaints)

Investigator: Cheryl Latham, PharmD, RPh

Supervisor: Samuel J. Penta, RPh

Allegation of Complaint: give nature code and summarize the allegations:

The complainant (a specialty pharmaceutical company) alleges that Ameridose, LLC located on 50 Fountain Street in Framingham (DS3467; no prior complaints) and Ameridose, LLC located on 20 Flanders Road in Westborough (DS89641; no prior complaints) manufacture and distribute an unapproved, pre-mixed nicardipine injection product. The complainant further alleges that the manufacture of this product "is unavoidably dangerous under the conditions of its use and poses an immediate risk of death for critically ill patients to whom it is administered."

Nicardipine injection is a calcium channel blocker indicated for "the short-term treatment of hypertension when oral therapy is not feasible or not desirable."

There are two forms of nicardipine injection approved by the FDA. The first is nicardipine (2.5 mg/ml) in 10 ml glass ampoules, for dilution in 240 ml of intravenous fluid. It is available as Cardene IV from [REDACTED] Inc and from various generic manufacturers. The second is Cardene I.V. Premixed Injection. It is supplied as a single-use, ready-to-use, iso-osmotic solution for intravenous administration in a 200 mL Galaxy ® container with 40 mg (0.2 mg/mL) nicardipine hydrochloride in either dextrose or sodium chloride. The pre-mixed bags are manufactured by Baxter Healthcare Corporation and marketed by [REDACTED]

Ameridose manufactures its pre-mixed nicardipine injection product by obtaining nicardipine ampoule products from hospital customers and by admixing the hospital's own nicardipine into commercially available diluent bags. Ameridose returns the finished products to hospitals, which store the bags until needed.

The complainant states that once diluted, nicardipine solution has a very short, 24-hour stability period at room temperature. The complainant further states, "Ameridose's practice of simply admixing nicardipine from approved ampoule products into an off-the-shelf I.V. bag cannot result in a ready-to-use nicardipine injection product that will be safe, pure, and stable beyond the 24 hour period specified in the FDA-approved labeling for ampoule products." The complainant continues, "The percent of nicardipine remaining in solution decreases as function of pH over a twenty-four hour period." The pH, concentration of the active ingredient, and the composition of the container material affect the stability of the active ingredient and the formation of impurities.

Activities and Findings:

On July 8, 2010 Board Investigators, with FDA Investigators, performed a site visit of both Ameridose's Framingham (DS3467; no prior complaints) and Westborough, Massachusetts (DS89641; no prior complaints) facilities. The MOR of the Framingham facility was identified as Sophia Pasedis (PH20217; Issued 06/24/1987; no prior complaints); the MOR of the Westborough facility was identified as Bryan M. O'Neill (PH23692; Issued 06/23/1997; no prior complaints).

At the time of the visit, the Framingham facility located on 50 Fountain Street in Framingham, MA was undergoing renovations with very limited operations and staff on site.

The Westborough facility, located on 20 Flanders Road in Westborough, was fully operational. An inspection was conducted of the facility's retail pharmacy license. No violation of Board of Pharmacy rules or regulations was found.

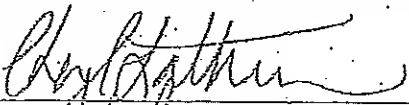
In a written response to [REDACTED] allegations dated July 15, 2010, Ameridose states, "Ameridose does not manufacture this product, but rather its pharmacists are admixing the hospital's own Nicardipine into a commercially available diluent bag just as the hospital pharmacist would but rather in a far more controlled and advanced cGMP environment." Ameridose also states that "multiple stability studies, completed by independent, FDA registered labs, which show that the admixed version(s) of Nicardipine admixed by Ameridose on behalf of its client hospitals, meet all stability, pH, sterility and other final admixed product requirements."

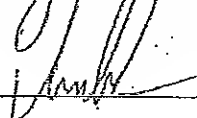
Ameridose further states that they have "hundreds of studies that address the sterility of its admixed medications" and that all admixing occurs "in ISO 5 environments inside state of the art clean rooms." Ameridose, continues, "Ameridose's operations exceed the requirements of USP <797> and meet cGMPs."

In a written, signed letter dated January 14, 2011, [REDACTED] stated that [REDACTED] and Ameridose, LLC ("Ameridose") have reached an amicable resolution to the companies' dispute regarding Ameridose's activities involving nicardipine."


The letter continues, "Accordingly, [REDACTED] no longer believes that any governmental investigative or enforcement actions against Ameridose are necessary to protect the public health

and safety and hereby withdraws its request that the Board of Registration in Pharmacy take any such actions."

Investigator Signature:  Date: 02/10/11

Supervisor Signature:  Date: 2/10/11

Addendum:

Investigator Penta spoke with FDA Investigator  on February 9, 2011. Per Investigator Emerson, at this time the FDA is not moving forward on this matter and the matter is administratively closed. If the matter is re-opened we will be contacted by FDA.



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June 30, 2010

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VIA E-MAIL AND OVERNIGHT DELIVERY

James D. Coffey, Director
Board of Registration in Pharmacy
239 Causeway Street, 2nd Floor, Suite 200
Boston, MA 02114

Re: Complaint Against Ameridose LLC for Unlawful
Manufacturing and Distribution of
Pre-Mixed Nicardipine Injection Products

Dear Mr. Coffey:

On behalf of [REDACTED] I am writing to call your attention to serious violations of Massachusetts pharmacy laws and regulations by Ameridose, LLC ("Ameridose"), of Framingham and Westborough, Massachusetts, and to request that prompt investigation and disciplinary actions be taken against Ameridose by the Board of Registration in Pharmacy (the "Board").

The unlawful actions of Ameridose involve the manufacturing and distribution of an unapproved injectable prescription drug product – specifically a pre-mixed nicardipine injection product – which is unavoidably dangerous under the conditions of its use and poses an immediate risk of death for critically ill patients to whom it is administered.

As indicated below, Ameridose is a Massachusetts-based company with two Massachusetts facilities, and holds six Massachusetts Pharmacy Licenses:

Ameridose, LLC
50 Fountain Street
Framingham, MA 01702
Phone: 888-820-0622
Phone: 508-656-2649
Fax: 508-872-0044

Ameridose, LLC
205 Flanders Road
Westborough, MA 01581
Phone: 888-820-0622
Phone: 508-656-2649
Fax: 508-872-0044

Mass. Pharmacy Licenses:
DS3467 (Retail Drug Store)
CS3467 (Controlled Substance)
CF3467 (Cert. of Fitness)

Mass. Pharmacy Licenses:
DS89641 (Retail Drug Store)
CS89641 (Controlled Substance)
CF89641 (Cert. of Fitness)



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Thus the Board has jurisdiction, and the legal obligation, to investigate this matter and take appropriate disciplinary action to enforce the law and protect the public health.

I. BACKGROUND – NICARDIPINE INJECTION PRODUCTS

A. FDA-Approved Products

Nicardipine injection products are indicated for “the short-term treatment of hypertension when oral therapy is not feasible or not desirable.” In practice, nicardipine injections are administered to hospitalized patients with elevated blood pressure due to serious medical events such as stroke, aortic dissections, elevated blood pressure due to kidney disease, or central nervous system (CNS) injury, where rapid reduction of blood pressure as a life-saving intervention is warranted.¹

There are two forms of nicardipine injection approved by FDA pursuant to the federal Food, Drug, and Cosmetic Act (“FDCA”):

- Nicardipine (2.5 mg/mL) in 10 mL glass ampoules, for dilution in 240 mL of intravenous fluid; available from EKR as Cardene® I.V. (nicardipine for injection) and from various generic manufacturers. This form of nicardipine was first approved in 1992.
- Cardene® I.V. Pre-Mixed Injection 20 mg or 40 mg (0.1mg/mL or 0.2 mg/mL), in 200 mL Galaxy® bags (“Cardene® RTU”). For each strength of Cardene® RTU there are two diluent solution options: dextrose or sodium chloride. This product form was approved in 2008.

B. Ameridose’s Unapproved Nicardipine Injection Product

Ameridose manufactures its pre-mixed nicardipine injection product by obtaining nicardipine ampoule products from hospital customers, diluting and filling the modified product into off-the-shelf I.V. bags, and returning the finished product to hospitals which store the bags until needed. The Ameridose product is not FDA-

¹ See P.E. Marik & J. Varon, 131 *CHEST* 1949–62 (2007); A.I. Qureshi, 118 *Circulation* 176–87 (2008); A.M. Pancioli, 51 *Ann. Emerg. Med.* S24–S27 (2008).



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approved, and as discussed below, it is unavoidably dangerous under the conditions of its use, poses an immediate risk of death for patients to whom it is administered, is misbranded and deceptive, and is being unlawfully manufactured and distributed in violation of the FDCA and Massachusetts law.

II. AMERIDOSE'S PRE-FILLED NICARDIPINE INJECTION PRODUCT POSES SERIOUS SAFETY RISKS

A. Nicardipine Injection Ampoules Have Very Short Stability After Being Filled Into I.V. Bags

The major drawback of nicardipine ampoules is that the product requires dilution with 240 mL of a suitable intravenous fluid before being administered by slow infusion at a final concentration of 0.1 mg/mL. Importantly, once diluted, the nicardipine solution has a very short, 24-hour stability period at room temperature. As the FDA-approved labeling for Cardene® I.V. ampoules (and equivalent generic products) warns, "THE DILUTED SOLUTION IS STABLE FOR 24 HOURS AT ROOM TEMPERATURE" (capital letters in original). Thus, for both safety and efficacy reasons, hospitals must wait until they have an identified patient in need of the drug before diluting the drug and filling it into an I.V. bag for immediate administration. Ameridose's practice of simply admixing nicardipine from approved ampoule products into an off-the-shelf I.V. bag cannot result in a ready-to-use nicardipine injection product that will be safe, pure and stable beyond the 24 hour period specified in the FDA-approved labeling for the ampoule products.

B. Ameridose's Manufacturing Process Cannot Overcome the Short-Stability Problem

The short-stability problem of diluted nicardipine ampoules, as well as difficulties in producing a sterile pre-filled nicardipine I.V. bag, posed technical barriers to the development of a pre-mixed ready-to-use product. However, through extensive research and development efforts, ~~was~~ was able to develop Cardene® RTU as the first and only shelf-stable² and sterile pre-mixed ready-to-use nicardipine injection product. FDA approved Cardene® RTU in 2008. And, reflecting the novelty of Cardene® RTU, and the innovation required to develop and produce such a product,

² Unlike diluted solution created using nicardipine ampoules, the Cardene® I.V. Premixed solution has a stable room temperature shelf life of up to two years.



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the U.S. Patent and Trademark Office ("PTO") issued U.S. Patent No. 7,612,102 (the '102 Patent) which covers pre-mixed ready-to-use nicardipine solution drug products.³ The '102 patent describes the technical difficulties that must be addressed in order to product a safe and stable pre-mixed nicardipine product as follows:

The production of stable, ready-to-use, premixed pharmaceutical compositions comprising nicardipine and/or its pharmaceutically acceptable salts as the active ingredient presents different development hurdles than does the development of the concentrated ampul product sold commercially as Cardene[®] RTM^[4] I.V. As shown in FIG. 1, the percent of nicardipine remaining in solution decreases as function of pH over a twenty-four hour period. The percent decrease in nicardipine varies with the diluent and container chosen by the hospital staff.

As described in the Examples, pH, the concentration of the active ingredient, and the composition of the container material affect the stability of the active ingredient and the formation of impurities. Thus, the development of a stable, ready-to-use premixed pharmaceutical composition requires simultaneous optimization of pH and nicardipine hydrochloride concentration, as well as selection of a pharmaceutically compatible container.

³ '102 Patent, § 5.2 (emphasis added).

solved the stability and sterility problems for pre-mixed nicardipine products through a combination of a modified pH range and the use of specially-designed Galaxy[®] I.V. bags, filled using Baxter's proprietary "Seal/Fill/Seal" aseptic manufacturing process. In the Galaxy[®] Seal/Fill/Seal process a special PL 2501 plastic film is sterilized by passage through a hydrogen peroxide (H₂O₂) bath in the Galaxy[®] machine, and the bulk solution, film, and closure components are brought together and assembled within the interior of the Seal/Fill/Seal machine. Because

³ A copy of the patent can be viewed at <http://patft.uspto.gov/nctacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PAII&p=1&u=%2Fntabhtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=7,612,102.PN&OS=PN/7,612,102&RS=PN/7,612,102>.

⁴ Here, "RTM" stands for "Ready-to-Mix."



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nicardipine is especially light-sensitive, the Galaxy[®] bag for the finished Cardene[®] RTU product uses an opaque outer film to protect the product from light-induced degradation. These processes and components for producing a shelf-stable and sterile pre-filled nicardipine product were extensively studied by [REDACTED] and the data and results were reviewed by the FDA in connection with the approval of [REDACTED] NDA for the Cardene[®] RTU product. See NDA 19-734/S-013 and S-014. No such FDA review has been conducted with respect to Ameridose's manufacturing processes and product components.⁵

Nicardipine ampoule products are sterile when manufactured, but that sterility is broken immediately upon opening the ampoule for dilution and filling into an I.V. bag. Where the diluted product is used immediately after being mixed, no sterility-related safety concerns would be expected. However, a pre-filled nicardipine I.V. bag that is not intended for immediate use could pose safety problems unless the entire contents and components of the product are appropriately sterilized.

[REDACTED] is unaware of what, if any, sterilization processes Ameridose uses for its pre-filled nicardipine product, but it is important to note that terminal sterilization techniques may not be safe and effective for such products. In its development work for the Cardene[®] RTU product, [REDACTED] studied the use of terminal sterilization with alternative I.V. bag systems but as [REDACTED] reported to FDA in its New Drug Application ("NDA") for Cardene[®] RTU, "[t]erminal sterilization . . . impacted nicardipine hydrochloride concentration and impurity levels to an extent that development of a commercially viable terminally sterilized nicardipine hydrochloride premixed product was not feasible." NDA No. 19-734/S-013, Module 2, Table P.2.2-2. The fact that Ameridose may be using sterilization techniques that have not been reviewed or approved by FDA and which may actually exacerbate the product's stability and impurity levels should be especially concerning to the Board.

C. Ameridose's False and Misleading Stability Claims

Ameridose cannot assure the safety of its pre-filled nicardipine I.V. bags. By filling its bags at a remote location and then shipping them to its hospital customers, it is

⁵ It is notable that Ameridose has had manufacturing problems in the recent past, specifically, a 2008 recall of pre-filled fentanyl I.V. bags due to super-potency. See FDA Enforcement Report at www.fda.gov/Safety/Recalls/EnforcementReports/2008/ucm120532.htm.



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inevitable that most if not all of Ameridose's products will be used in patients far longer than 24 hours after being filled, and thus will be beyond the documented stability period for diluted nicardipine ampoules. Yet despite the serious life-threatening risk to patients posed by degraded nicardipine injection products, Ameridose's business model reflects its intent that its products be stored in hospital inventories for weeks before use. This intended use is further evidenced by the fact that, to [REDACTED] understanding, Ameridose represents, through altered and unapproved labeling, and/or oral representations by Ameridose sales agents, that its pre-mixed nicardipine products has 75 days of shelf-life stability. This claim is directly contrary to the stability warning and instructions in the approved labeling for nicardipine ampoule products that Ameridose uses to create its pre-mixed product, and BKR is not aware of any scientifically sound bases to support extended stability dating for Ameridose's pre-mixed product.

II. THE AMERIDOSE PRODUCT IS UNLAWFUL UNDER MASSACHUSETTS LAW

Ameridose's manufacturing and distribution of its pre-mixed nicardipine injection product violates Massachusetts law and the Board's regulations, specifically, the Code of Conduct for Registered Pharmacists, Pharmacies and Pharmacy Departments (the "Code of Conduct"), 247 Code of Massachusetts Regulations § 9.01, law in several ways.

A. Nonconformity With Federal Law in Violation of § 9.01(1).

The Code of Conduct, § 9.01(1), requires that "a registered pharmacist shall at all times conduct professional activities in conformity with federal, state and municipal laws, ordinances and/or regulations, including the regulations of the Board." Ameridose is in violation of § 9.01(1) because its pre-mixed nicardipine injection product violates federal law. Specifically, the Ameridose product is a "new drug"⁶ and because it is not the subject of an approved New Drug Application, the product violates the FDCA. See 21 U.S.C. §§ 355(a) (requiring FDA approval of all "new drugs"), 331(d) (prohibiting distribution of an unapproved new drug in violation of § 355). Moreover, the fact that Ameridose modifies FDA-approved nicardipine ampoules violates FDA regulations which require prior FDA approval for the types

⁶ See 21 U.S.C. §§ 321(p) (defining "new drug"); see also *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug").



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of changes Ameridose makes in converting nicardipine ampoules into pre-filled I.V. bags. *See* 21 C.F.R. § 314.70(b).⁷

B. Dispensing a Drug in a Manner Intended
To Circumvent Law in Violation of § 9.01(2).

The Code of Conduct, § 9.01(2), also prohibits a pharmacist from dispensing a drug "in a manner which is intended, either directly or indirectly, to circumvent the law." By modifying nicardipine ampoules into pre-mixed I.V. bags without FDA approval, Ameridose is, directly or indirectly, circumventing the very FDA regulations that BKR followed in order to obtain approval of its NDA, and thus violates § 9.01(2).

Moreover, Ameridose's product is essentially an attempted (and unapproved) copy of a commercially available product – Cardene® RTU – that FDA has carefully reviewed and approved for safety and efficacy. As FDA itself has stated, this type of activity "circumvents important public health requirements and undermines the drug approval process – the evidence-based system of drug review that consumers and health professionals rely on for safe and effective drugs."⁸

In addition, any representation by Ameridose that its product is a "pharmacy compounded" product exempt from FDA regulation would be false and would also reflect an intent to circumvent the requirements of federal law. FDA has long recognized the deceptive and evasive intent of some companies claiming to be

⁷ Under this regulation, prior FDA approval is required for "any change in the drug substance, drug product, production process, quality controls, equipment, or facilities," including,

- "changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients. . . ."
- "changes that may affect drug substance or drug product sterility assurance. . . ."
- "changes in a drug product container closure system that controls the drug product delivered to the patient or changes in the type. . . (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) . . . of a packaging component that may affect the impurity profile of the drug product. . . ."

⁸ Statement of Steven K. Galson, CDER, "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients," before the S. Comm. on Health, Ed., Labor, and Pensions (Oct. 23, 2003) (emphasis added).



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"compounding pharmacies," as described in the agency's Compliance Policy Guidance on Pharmacy Compounding (the "Compounding CPG");

Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies.

* * *

[W]hen the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action.⁹

C. Deceptive Acts in Violation of § 9.01(6)

The Code of Conduct, § 9.01(6), requires that "[a] pharmacist shall not engage in any fraudulent or deceptive act." Ameridose is committing deceptive acts in violation of § 9.01(6) because, to [REDACTED] understanding, Ameridose represents, through new labeling, sales representative statements, or otherwise, that the product is stable for 75 days from the date of its manufacture when in fact, according to FDA, a diluted nicardipine ampoule product is not stable beyond 24 hours. Ameridose's representations regarding extended stability of its product are therefore deceptive in violation of Code of Conduct § 9.01(1), and also render the product misbranded in violation of the FDCA, which provides that a drug product is misbranded "[i]f its labeling is false or misleading in any particular," or if "it is dangerous to health when used in the dosage or manner...suggested in the labeling thereof." 21 U.S.C. §§ 352(a), 352(j).

⁹ FDA Compliance Policy Guide Manual, § 460.200 (2002).



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D. Distributing Expired, Outdated and
Substandard Drugs in Violation of § 9.01(10)

The Code of Conduct, § 9.01(10), also generally prohibits pharmacists from "dispens[ing] or distribut[ing] expired, outdated or otherwise substandard drugs...." As described above, Ameridose's pre-mixed nicardipine injection product expires and becomes outdated a mere 24 hours after it is mixed, yet as distributed by Ameridose and used by hospitals, the product is not used in patients until days or weeks after it has expired. Thus, Ameridose is also violating Code of Conduct section 9.01(1) by its manufacturing and distribution of its pre-mixed nicardipine injection product.

III. THE BOARD CAN AND SHOULD TAKE PROMPT
DISCIPLINARY ACTION AGAINST AMERIDOSE

Under the Code of Massachusetts Regulations, 247 CMR 10.03(1), "the Board may impose disciplinary action against an individual or entity licensed or registered by the Board" for violations of the pharmacy laws or regulations, or on one or more other grounds, including:

"(k) Engaging in conduct that has the capacity or potential to place the public health, safety or welfare at risk;" and

"(l) Engaging in conduct that has the capacity or potential to deceive or defraud."

247 CMR § 10.03(k) & (l).

Both of these bases for disciplinary action apply in this case. As described above, Ameridose's pre-mixed nicardipine injection product is unsafe, and puts the public health at risk, because its extremely short stability period means that patients who receive the drug will be receiving an expired, outdated, and substandard product. Moreover, because Ameridose represents that its product is safe and stable for much longer than 24 hours after being filled, when in fact the FDA has determined that the product is stable for no more than 24 hours, Ameridose's activities are deceptive.



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CONCLUSION

Ameridose's unapproved pre-filled nicardipine LV product is unsafe and unlawful, and the Board should take immediate action to prevent further distribution of this product.

Please contact the undersigned if you have any questions or require additional information.

Respectfully submitted,

Jim Czaban

James N. Czaban

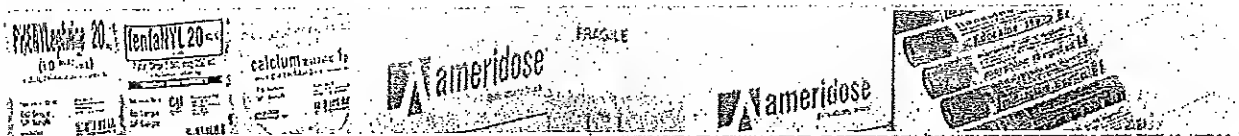
Nathan S. Cardozo

cc:





PRODUCTS



Ameridose offers over 2,200 sterile admixed IV solutions and prefilled oral syringes so that we are able to meet all your hospital pharmacy outsourcing needs. If you are already an Ameridose customer, you will find our full catalog through your secure online customer portal.

If you are new to Ameridose, an Ameridose representative would be pleased to provide you with greater detail on our offerings. Simply call 1-888-820-0622.

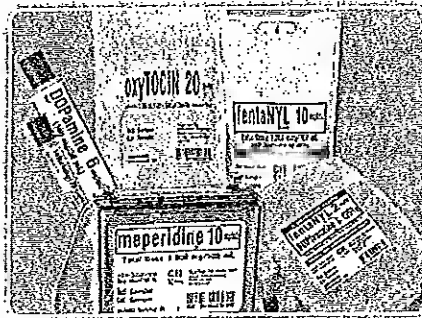
Sterile Admixing Services

Managed by licensed pharmacists with extensive hospital experience, Ameridose is uniquely qualified to deliver outsourced solutions to hospital pharmacists who face increasing demands on their resources.

Ameridose's extensive facilities are custom designed and constructed with keen attention to environmental quality and control. Our preparations undergo rigid real-time stability studies using stability-indicating methodologies by third-party, independent FDA registered laboratories for a wide range of criteria including stability and sterility.

Ameridose can provide the admixed and repackaged solutions that you need for categories including:

- Antagonist
- Antibiotic
- Anticholinergic
- Cardiac Medication
- Electrolyte
- General Anesthetic
- Heparin
- Labor and Delivery Needs
- Local Anesthetic
- Neuromuscular Blocking Agent
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